

EVALUATION OF PATIENTS WITH ACUTE  
CORONARY SYNDROMES USING CARDIAC  
MAGNETIC RESONANCE IMAGING AND  
BIOELECTRICAL AND BIOCHEMICAL MARKERS

by

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## **MD thesis - Edinburgh University**

I declare that the work that comprises this thesis is my own.

I declare that this work has not been submitted for any other degree or professional qualification.

Signed

Dr Thomas N Martin

## ABBREVIATIONS

**ACS** Acute coronary syndrome  
**AMI** Acute myocardial infarction  
**CABG** Coronary artery bypass graft  
**CeMRI** Contrast enhanced cardiac magnetic resonance imaging  
**CINE** Cinematographic  
**CK** Creatine kinase (IU/L)  
**CK-MB** Creatine kinase MB fraction (IU/L)  
**CRP** C-reactive protein (mg/L)  
**DE** Delayed hyperenhancement, refers to either an area or the total mass (g)  
**ECG** 12 lead Electrocardiogram  
**Gd-DTPA** Gadolinium - diethylenetriamine pentaacetic acid  
**LAD** Left anterior descending coronary artery  
**LCx** Left circumflex coronary artery  
**LA** Long axis  
**LV** Left ventricle  
**LVEF** Left ventricular ejection fraction (%)  
**LVESV** Left ventricular end systolic volume (ml)  
**LVEDV** Left ventricular end diastolic volume (ml)  
**LVM** Left ventricular mass (g)  
**LVOT** Left ventricular outflow tract  
**MVO** Microvascular obstruction  
**PCI** Percutaneous coronary intervention  
**RCA** Right coronary artery  
**SA** Short Axis  
**SPECT** Single photon emission computed tomography  
**SSFP** Steady state free precession  
**TI** Inversion time  
**True FISP** Fast imaging with steady precession (Siemens)  
**TnI** Troponin I (ng/ml)  
**WCC** White cell count ( $\times 10^9/l$ )

# 1 Abstract

**Introduction:** Cardiac disease is a major cause of morbidity and mortality worldwide and therapeutic advances continue to be made. Improved accuracy of diagnosis and risk stratification is therefore important. Advanced imaging using contrast enhanced magnetic imaging (ceMRI) is under investigation for assessment of myocardial necrosis in both acute and chronic settings due to ischaemic and non-ischaemic aetiologies. Consecutive patients with an incident episode of chest pain necessitating hospital admission were recruited and underwent ceMRI. CeMRI was considered the gold standard for determining presence of ischaemic myocardial necrosis and used to evaluate current ECG guidelines in acute chest pain syndromes. ST segment elevation on the presenting ECG determines the acute reperfusion strategy but will not detect all infarcts and additional consideration of ST depression termed, “STEMI equivalent” may reduce the burden of missed AMI. Infarct size (IS) was measured by manual planimetry of regions of delayed hyperenhancement (DE) and then correlated with routinely available biochemical and bioelectrical markers. The evolution of infarct size and characteristics were then followed using ceMRI at 4 time points out to 1 year. The role of inflammation in MI using CRP as the marker was also investigated. Finally, additional clinical information was provided by performing ceMRI in this group of patients and the findings are presented.

## 2 Foreword

Coronary heart disease is a major cause of morbidity and mortality in the Western world with Scotland, Glasgow in particular, near the top of the MONICA league tables (1). The ultimate consequence of coronary heart disease is myocardial infarction so it is important to make an accurate diagnosis for physical, psychological and social reasons. Diagnostic criteria have been evolving since the World Health Organisation published the first guidelines in 1994 (2). These relied on the patient meeting two out of three from: typical chest pain; typical appearances on the 12-lead ECG; and a rise and fall of cardiac biomarkers. The introduction of assays to measure serum troponin meant that it assumed a central role when the joint European Society and American College of Cardiology published updated guidelines in 2000 (3) almost rendering the ECG and patient symptoms superfluous. By the time of discharge most patients admitted with chest pain will have a clear diagnosis using these basic tools. There a number of patients that would benefit from a more comprehensive examination of left ventricular function, infarct size and infarct characteristics.

An accurate, reproducible and safe method that would perform all these tasks at a single time point is desirable. Advanced imaging is therefore under investigation to improve the diagnosis of ischaemic heart disease at all stages of disease progression, but the first priority must be once it has become manifest. Contrast enhanced cardiac Magnetic Resonance Imaging (ceMRI) is non invasive and uses no radiation making it a very safe procedure to perform. CeMRI provides three dimensional cinematographic images allowing accurate and reproducible assessment of left ventricular mass, function and volumes. The addition of contrast agents such as Gadolinium-DTPA (Gd- DTPA) enables direct identification of

irreversible ischaemic injury. It is therefore possible to determine infarct size, location, transmural and endocardial extent. It is also possible to visualise infarct characteristics, such as the presence of microvascular obstruction, that are associated with additional adverse prognosis. ceMRI seems likely to become the gold standard reference imaging modality for myocardial infarction size but further work is still required. The ceMRI set up and running costs are high and it is not yet readily available in all hospitals so any additional roles it may play in Acute Coronary Syndromes (ACS) still require to be validated.

The hypothesis of this thesis is that quantitative and qualitative electrocardiographic and biochemical markers of myocardial necrosis, inflammation and remodelling in patients following their first myocardial infarction will correlate with infarct size as measured by ceMRI. In addition, ceMRI may provide information on those patients admitted with a chest pain syndrome but without a clear diagnosis of acute myocardial infarction.



## 3 Introduction

### 3.1 Background

Every year in the United Kingdom, around one million patients are admitted to hospital as an emergency with a chest pain syndrome. In 2004 the diagnosis of acute myocardial infarction (AMI) was made in 230 000 patients. The mortality from coronary heart disease was 105 000 accounting for 21% of male and 15% of female deaths. In 2006 the total annual cost to the UK economy of coronary heart disease was £7900 million, £3500 million was attributable to hospital care and £4400 million to work days lost and informal care (4).

Coronary heart disease forms a major part of the work of NHS Scotland accounting for 4% of all hospital discharges. For the year ending March 31st 2006 there were 48 962 hospital discharges for coronary heart disease, 16 320 of whom were diagnosed with acute myocardial infarction.

Within the greater Glasgow Health Board area, for the 2 years that covered this study's recruitment period (2002 and 2003), the crude annual rate for AMI per 100 000 population was 276.8 and 273.1 respectively (5). Patients enrolled in this study were recruited from the population of 1278 patients admitted to the Western Infirmary, Glasgow to rule out AMI between August 2002 and May 2003. Five hundred and nineteen (41%) had a discharge diagnosis of ACS.

Patients are encouraged to attend hospital as an emergency if they experience chest pain of greater than 20 minutes duration. Not all patients have typical symptoms; some have none that

can be recognised as indicative of ischaemic heart disease. It is important to achieve a rapid and accurate diagnosis regarding AMI in patients with suggestive symptoms so that prompt reperfusion therapy may be administered. Cardiac biomarkers such as troponin are sensitive but the infarct process is near completion by the time they are available. The initial ECG is therefore the cornerstone of determining the initial management. Those patients with ST elevation (STEMI) will receive prompt reperfusion therapy with either thrombolysis (the primary method in this study) or percutaneous intervention (PCI). The remaining patients (Non-STEMI) may not.

The aim of acute reperfusion therapy is to restore blood flow through an open epicardial artery and to limit final infarct size. However, it is well recognised that an open artery does not necessarily equate to perfusion at the tissue level due to microvascular obstruction (MVO) (6-8). In addition, any area that is reperfused will include both infarcted and stunned myocardium, so reperfusion itself can adversely affect infarct size. Final infarct size is determined by a number of factors including the amount of tissue perfused by the occluded artery, the duration of occlusion, quality of reperfusion, perfusion by collaterals, and ischaemic preconditioning.

It is of clinical importance to make an accurate estimate of infarct size in vivo as the extent of damage is closely related to a patient's prognosis (9-11). Knowledge of infarct size will improve risk assessment and guidance of future management. It also serves as an end point in the evaluation of current and future reperfusion therapies. The evolution of the myocardial scar with time may also be of clinical importance. Infarct healing is an ongoing process with initial infarct expansion due to oedema and haemorrhage followed by resorption and collagen formation. To be able to document the natural history of infarct healing will be of benefit in

future therapeutic trials such as rebuilding myocardial tissue at the infarct site using stem cell therapy.

The current estimates of infarct size are limited to cardiac biomarkers, the ECG and echocardiography in clinical practice.

The initial and most validated biomarker was the cytoplasmic enzyme creatine kinase (CK) (12;13). Its release is affected by reperfusion, requires serial measurements and lacks cardiospecificity although the latter was improved by the MB fraction (CK-MB) (14). CK has largely been superseded by measurement of troponins (T and I), the structural protein of the myofilament exclusively expressed in cardiomyocytes. The release ratio of troponin is unclear and values remain elevated for up to two weeks. Previous correlations with infarct size have shown it to be superior to CK or CKMB (15;16).

The standard 12 lead ECG is widely available and has been used for many decades as a guide to the extent of threatened or damaged myocardium in acute and chronic myocardial infarction. Selvester et al (17) developed a 31 point quantitative QRS scoring system to be applied to the standard 12 lead ECG for the estimation of MI size and location. This score was devised in the pre reperfusion era of the early 1980s using autopsy samples. It is testament to the score that it has only undergone minor adjustments since, although validation has so far been limited to comparison with indirect measurements (18-20) in vivo or histopathology ex vivo(21;22).

Trans thoracic echocardiography (TTE) is able to assess global and regional wall function but these measurements of infarct size are indirect and influenced by image quality, the presence of

arrhythmias, cardiomyopathies, valvular heart disease and ventricular loading conditions (23). TTE can also overlook small subendocardial infarcts and its sensitivity is reduced in the acute setting due to stunning or hibernation. There will be no formal comparisons made between TTE and ceMRI in this study.

Gibbons et al in 2004 reviewed the potential value of many clinical methods for “quantification of infarct size”; and concluded that “on the basis of existing evidence single photon emission computed tomography (SPECT) sestamibi imaging is currently the best technique available to meet this challenge” (24). A number of animal and clinical studies have been conducted using SPECT. The technique is well validated in the determination of final infarct size (25-28) and there is comparability between multiple centres(29) but it is not routinely used acutely in the UK. SPECT has the major disadvantage that radiation is required.

CeMRI, as a contender to the status of new gold standard has been compared with SPECT imaging (30-32). The main conclusions are that ceMRI and SPECT are equivalent for infarct size quantification but that ceMRI has additional advantages in spatial resolution and lack of radiation. CeMRI provides the first clinical method to directly image the infarcted myocardium (33) making it possible to comment on certain characteristics of the infarct.

A systemic inflammatory response has been demonstrated across the spectrum of ACS and C Reactive Protein (CRP) is the most widely studied and readily available marker. The source of CRP is not clear and it is uncertain whether CRP is the cart, the horse or both in AMI (34). CRP has been implicated in microvascular obstruction (35), so may have the ability to

differentiate infarct characteristics that would provide an explanation for its additional prognostic information.

Several matrix metalloproteinases are expressed in the myocardium and may play a role in pathogenesis of LV remodelling after AMI by degrading myocardial collagen. MMP-1 transcription is increased post AMI which may be due to a functionally specific polymorphism in the promoter sequence. It would be possible to measure the phenotype using ceMRI due to its accuracy and reproducibility at measuring LV dimensions.

By the time of discharge most patients will have a correct diagnosis of AMI or unstable angina and the subsequent management plan is dependent on a sound assessment of the patient's prognosis (36). The label of myocardial infarction has been redefined since the introduction of troponin (37) but this only provides information on at most a 2 week window. Missing the diagnosis of current (or prior) MI deprives patients of the proven benefits of secondary prevention medical therapy, let alone revascularisation. On the other hand, a mis-diagnosis of MI will have implications including lifelong drug treatment and raised insurance premiums. Women in particular present with atypical symptoms of AMI and would be more likely to be unrecognised than in men (38;39). It has been shown that, by the presence of pathological Q waves, up to 25% of myocardial infarctions are silent (40) and that the true prevalence may be even higher due to its insensitivity (41).

Acute coronary occlusion is not the sole cause of myocyte necrosis and there are other acute medical disorders that are associated with a positive troponin. In many patients the diagnosis is clear from the routine clinical history and investigations performed in the acute medical ward.

Not all patients are discharged with a clear diagnosis and, “chest pain, unknown cause” is the label often (mis)used.

CeMRI is an advanced imaging tool that can be used to accurately measure LV dimensions and to diagnose, quantify and characterise myocardial infarction both on admission and on serial examinations. This allows novel markers of remodelling to be assessed and comparisons to be made with the current biochemical and bioelectrical measures of infarct presence and size. It will enable investigation into the relationship of CRP to infarct size and microvascular obstruction. Finally, for those patients admitted with chest pain who do not meet the current criteria for AMI, ceMRI will describe the myocardial structure and function in more detail that may provide additional diagnostic information.

### **3.2 Contrast enhanced cardiac Magnetic Resonance Imaging in acute and chronic myocardial infarction**

Cardiac magnetic resonance imaging allows accurate and reproducible three dimensional quantification of cardiac structure and function, in particular the left ventricle (LV) (42). With the addition of the extracellular contrast agent Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA), direct visualisation of myocardial damage with high spatial resolution is possible as delayed hyperenhancement (DE). CeMRI therefore provides a unique gold standard for evaluation of more universally available diagnostic methods (43).

#### **LV mass and function**

CeMRI offers accurate and reproducible measurements of the routine parameters of global cardiac function with several advantages over TTE. There is excellent delineation of both endocardial and epicardial borders and a user defined choice of imaging plane. A three dimensional cinematographic image of the LV for measurement comprises a stack of short axis (SA) slices so no geometrical assumptions are required. There are analysable images in the vast majority of patients, which compares favourably to TTE where up to 30% of images are of too poor quality to measure LV function and dimensions objectively. The standard global measurements are: LV ejection fraction (LVEF), LV end diastolic volume (LVEDV), LV end systolic volume (LVSEV) and LV mass (LVM). LVEF is the universal parameter for LV performance and is a function of the dimensions LVEDV and LVESV whose change over time have prognostic significance, a process known as remodelling.

Other measurements that would be possible using the dataset acquired include diastolic function, myocardial viability and RV structure and function. Due to the additional time and

software required this information will not form part of the thesis. The raw data is available and could still be analysed for future studies.

Stress ceMRI was not performed in the Glasgow Cardiac Magnetic Resonance Unit (GCMRU) at the time of this study so there will be no data on this. It will be possible to provide resting viability information on these patients at a later date but no such data on will be presented in this thesis.

In summary the global LV structure and function was measured in all patients at all visits. The global LV function is part of a routine ceMRI scan and forms part of the secondary analysis in this study.

### **Contrast enhanced cardiac magnetic resonance imaging**

To achieve image contrast in ceMRI, T1 weighted images were used to show the difference in longitudinal relaxation times between adjacent pixels. The contrast agents used work by shortening the T1 relaxation time in the contrast-rich tissue so the measured signal after the second radiofrequency pulse is greater than that of the contrast-poor tissue. Using gadolinium based contrast agents and ECG gated spin echo sequences, it was noticed that the image intensity of myocardial infarction was particularly strong (hyperenhanced or bright white) when obtained >10 minutes after injection. There was a major problem with image quality because only one line of k space was filled per cardiac cycle. Each scan had a very long acquisition time (minutes) leading to respiratory motion artifacts.

There were two breakthroughs in the 1990's. The first was the ability to use segmented k space so that multiple lines could be acquired during each cardiac cycle thereby greatly reducing the



imaging time (44). The entire image could now be acquired in around 10 seconds or a single breath-hold. The second innovation was the use of an inversion recovery pre-pulse which increased the T1 weighting of images even further (45). For infarct imaging, the inversion time is set to null (black) normal myocardium thus further improving the differential by a factor of up to 500%. Waiting for 20-40 minutes after the injection of contrast and visualising infarction as a bright white area gave rise to the term delayed hyperenhancement (DE) which has emerged as a new reference method for infarct characterisation in vivo (46-50).

The area of DE accurately depicts infarction in animal models by comparison with triphenyltetrazolium chloride (TTC) stained gross histological slices of the heart, but no such studies have been performed in humans (51-54). Research in humans revealed that the transmural extent of hyperenhanced myocardium correlates with the probability, magnitude and timing of functional recovery after reperfusion in acute MI and chronic ischemic heart disease (48;55).

The mechanism for the different Gd-DTPA wash-in/wash-out profiles of necrotic and viable myocardium is under ongoing investigation. Current theories include: an increased distribution volume in the area of necrosis caused by loss of myocyte integrity and oedema in AMI; and scar tissue replacement in chronic MI (33;56-61). By using the ceMRI technique early after AMI the region of DE had been thought to overestimate the actual MI size because of the increased distribution volume of contrast due to acute oedema in the peri infarction zone (62). Detailed histological studies have since confirmed that the presence of hyperenhancement is strongly associated with infarct size by TTC staining in both acute and chronic infarcts (63). Pathologically, the initial infarct expansion during week 1 is due to oedema and haemorrhage

within the infarct zone followed by resorption up to 28 days and collagen formation until 6 months. To be able to document the natural history of infarct healing in vivo will be of benefit as an end point in future therapeutic trials that aim to influence infarct sizes. Serial ceMRI was performed on patients with first presentation of AMI at 4 time points associated with the major histopathological landmarks to determine the absolute and rate of change in infarct size and morphology.

### **Myocardial infarct characteristics**

It is not only possible to determine infarct size but qualitative information is available on different characteristics that have also been shown to influence prognosis (64-67). These characteristics include infarct location, transmural extent and MVO (31;68;69).

#### ***(i) Location***

The definition of infarct location was standardised in 2002 and the guidelines were released as a Scientific Statement by the American Heart Association (70). The aim was to use precise anatomic landmarks to divide the LV into segments that would correspond to standard coronary artery territories. There are 17 segments in this model and the 3 vessel territories are: left anterior descending artery (LAD), left circumflex artery (LCx) and right coronary artery (RCA).

#### ***(ii) Transmurality***

As a consequence of the high spatial resolution of ceMRI images it is possible to detect infarcts that are <1% total LV mass meaning that the transmural extent can be expressed as a proportion of myocardial wall thickness (43;60). This is a major advantage over SPECT imaging that can miss subendocardial infarcts (71). It allows differentiation between ischaemic

(involving the subendocardium) and non ischaemic (sparing the subendocardium) patterns of myocyte necrosis (72). The presence of DE is not specific to myocardial infarction; but when infarction is the cause, there is always involvement of the subendocardial layer. When there is DE that does not involve the subendocardium then different non ischaemic aetiologies have to be considered such as myocarditis, sarcoidosis, cardiomyopathy and iatrogenic scars.

There has been much debate about what constitutes a transmural infarct. Myocardial infarcts are a complex shape and within the same infarct there will be varying degrees of transmural involvement rendering the binary allocation over simplistic. The degree of transmural involvement has been shown to be inversely proportional to recovery of segmental function. The best recovery of global function was in those patients with no infarct or <25% transmural involvement and over 90% of akinetic or dyskinetic segments have a transmural involvement score of >50% (73-75). There are many ways of scoring transmural involvement and with continued improvement in post processing software including automated programmes any degree of precision is possible once the endocardial and epicardial contours have been delineated. At the time of this study it was only possible to visually score the extent of transmural involvement and good agreement has been shown with automated systems (74). Thus assessment of degree of transmural involvement and recognition of a subendocardial sparing pattern of DE is important in future clinical decision making.

### ***(iii) Endocardial extent***

It had not been possible to measure endocardial extent with any accuracy in vivo until the development of ceMRI. Myocardial infarct size is a function of its transmural involvement and endocardial extent so one should not be considered without the other. Endocardial extent has

been shown to be more predictive of pathological Q waves than transmural extent in a small study of first time reperfused myocardial infarcts using ceMRI (76).

#### **(iv) Microvascular obstruction**

MVO leads to inadequate myocardial tissue perfusion in an area subtended by an angiographically open coronary artery (6;8). MVO can occur in over 30% of patients after acute reperfusion therapy for AMI and is associated with poor functional and clinical outcomes when compared to patients with reflow post reperfusion (77;78). MVO arises due to platelet microembolism, thrombosis, neutrophil plugging, free radical release, endothelial dysfunction and microvascular constriction (79-83). The white cell count is an independent risk factor for, and correlates with extent of, coronary disease and the risk of reinfarction (84-86).

Lima et al. noticed that during ceMRI there was often a region of hypoenhancement at the core of the hyperenhancement which they described as regional heterogeneity (87). Some basic animal research has confirmed that these areas of hypoenhancement represent MVO by showing negative staining for thioflavin-S in histological photography under ultra violet light (54). MVO seen <5 minutes following GdDTPA injection shall be termed “early MVO” and has been shown to be associated with an adverse prognosis and reduced late functional recovery (65;88). By considering the images as part of the delayed enhancement (DE) protocol an improved distinction between hypo- and hyper- enhanced areas is achieved and will delineate areas with more profound microvascular damage, termed “late MVO” (67). Late MVO has been shown to be a more powerful predictor of major adverse clinical events than LV ejection fraction, infarct size and end diastolic volume (67).

MVO by ceMRI correlates with both standard measures of infarct size (CK) and inflammatory status as assessed by leucocytes and CRP in patients with STEMI treated with primary PCI (89). In the current study NSTEMI patients are also included and the primary acute reperfusion therapy was thrombolysis. Both early and late MVO are considered.

There is no doubt that MVO is a major hindrance to the success of reperfusion and specific therapies are limited. There is evidence for a central role of inflammation in ACS so the interactions between MVO and inflammation, infarct size and infarct healing were studied. The incidence, natural history and interactions of both early and late MVO identified by ceMRI are also described.

#### **(v) *CeMRI limitations***

There are a number of limitations to the routine performance of ceMRI in all patients admitted with acute chest pain to rule out myocardial infarction in addition to the cost and limited portability. The absolute contraindications to ceMRI scanning are covered in

MRI safety **Questionnaire, 12.4.** The patient factors include claustrophobia, which accounted for 5.7% of patients eligible for this study, and inability to lie flat for the scan duration (mean 40 minutes). Image quality is strongly affected by patient movement so their cooperation is required and they must be able to hold their breath for approximately 10 seconds. Images for DE are acquired during diastole, triggered by the ECG and reliant on a regular R-R interval so dysrhythmias including atrial fibrillation can affect image quality. The protocol for acquisition of images is standardised but significant adjustments are required to be made by the operator. The scans for this study were performed by one of 3 operators (TNM, TS, BAG) with 9 months of full time training prior to the first patient scan. A major limitation of ceMRI at the time of the study was the ability to determine the age of the myocardial damage although there have since been some promising studies in the use of T2-weighted imaging (90).

### 3.3 ST segment deviation and QRS complex patterns on the ECG in acute myocardial infarction

This section describes the current use of the ST segment on the admission ECG in the triage of patients with chest pain. The Selvester score utilising the QRS complex is described in the estimation of infarct size and previous studies using ceMRI are reviewed.

The admission ECG, particularly ST segment deviation, is used in the triage of patients but is only a snap shot of a short period of time. It is generally the gatekeeper to reperfusion therapy and Coronary Care Units, but up to 28% of patients with normal admission ECG are subsequently ruled in for MI (91). Missing the diagnosis of AMI on admission doubles the risk adjusted mortality and the ten year mortality from unrecognised MI has been estimated to be 45 to 55% (92;93).

Clinical decisions for initiating reperfusion therapy are typically based on criteria developed in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) series of trials (94). Slightly revised criteria have since been introduced by the American College of Cardiology and European Society of Cardiology (ACC/ESC) joint committee (95). It is well recognised that the sensitivities of these sets of ECG criteria are suboptimal (96;97) An example of this deficiency is the routine under detection of acute posterolateral myocardial infarction that is the typical result of occlusion of the left circumflex coronary artery (LCx) (98). The adverse risk associated with non-ST segment elevation myocardial infarction (NSTEMI) is well documented (99), but many trials have failed to demonstrate the benefits of thrombolysis on the basis of alternative non-ST segment elevation criteria (100-103). With the emergence of more targeted treatments whose benefits remain

time dependent, such as percutaneous coronary intervention, the role of the admission ECG as a triage tool is increased.

Acute transmural ischemia caused by occlusion of a major coronary artery produces an epicardial injury current that can be detected as a deviation of the ST-segment toward the involved myocardial region(104). This deviation is ST segment elevation when a region is “viewed” by the positive pole of an ECG lead but ST-segment depression when “viewed” by the negative pole. Acute occlusion of the left anterior descending (LAD) or the right coronary artery (RCA) therefore typically causes ST-segment elevation in chest leads V1 to V4 or in limb leads II, aVF, and III, respectively, and therefore the resulting myocardial infarcts are termed STEMI. However, acute occlusion of the non dominant LCx typically produces only ST-segment depression in the 12 standard ECG leads, and therefore, the resulting myocardial infarcts could be termed “STEMI equivalent” (105). This ST-segment depression in the standard leads would appear as ST-segment elevation in the negative counterparts of these leads (97;106) **Figure 3-1.**

Whilst ST segment deviation is useful in the acute setting and has been used to predict myocardium at risk (107) it is the QRS segment that provides information on the final infarct size. An area of myocardial infarction results in loss of local electrical sources resulting in a reduction in the QRS and STT potentials for that area. Therefore the ECG has the ability to identify, localise and quantify this important event. The amplitude and duration of these deformities in ECG leads perpendicular to the pre-existing local electrical fields are proportional to the amount of myocardium removed by the infarction. In order to use this information to determine infarct size the eponymous scoring system derived by Ronald



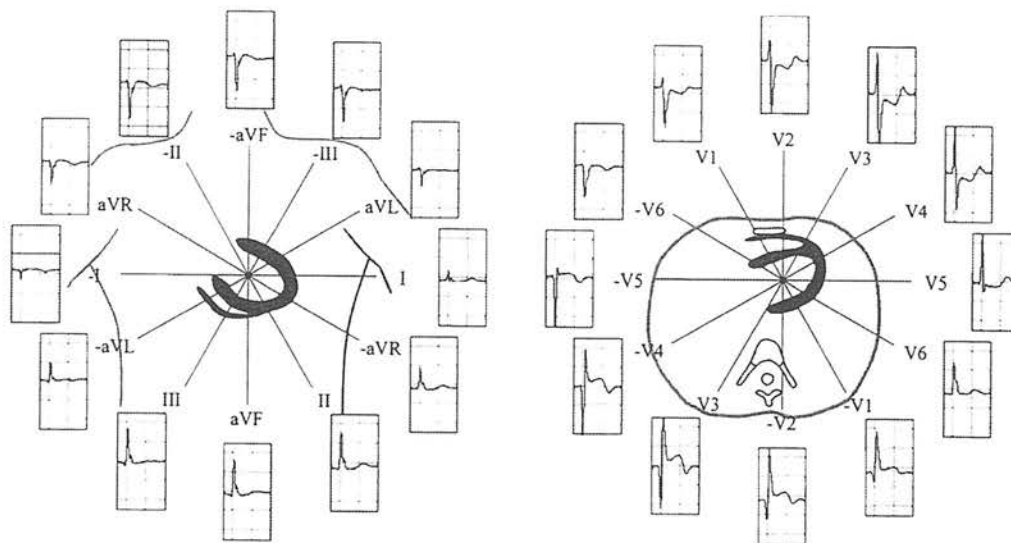


Figure 3-1: ECG recording from a patient during balloon inflation in the LCx with ST depression in V1 - V5 appearing as elevation in the negative counterparts

Selvester (108-112). This was validated by histopathology for different MI locations in the chronic phase of infarction prior to the reperfusion era. The Selvester QRS scoring system is weighted and considers not only Q waves but also other infarct related deformities in the QRS complex such as changes in the R wave and S wave amplitudes and durations. The ratios of R:Q and R:S are also considered **Appendix 12.1 Selvester Score**. Previous studies have documented the clinical use of the Selvester score in predicting prognosis(113).

Further development of ECG criteria requires valid non-ECG methods to define the size of the initial myocardium at risk, the final infarct size and the function of the salvaged myocardium. Several studies have confirmed that the Q wave is a marker of infarct size rather than transmural extent using ceMRI as a gold standard (114). In the acute setting of reperfused

first time AMI the global QRS score at one week has been shown to correlate with MI size, MI transmural extent and MI endocardial extent (76;115). The Selvester QRS scoring system has been validated in chronic anterior myocardial infarctions using a ceMRI gold standard and the correlation is particularly strong in the mid ventricular segments (116).

The concept of ceMRI as a gold standard in the validation of ECG scoring systems is relatively unique. Based on the data from this thesis a group was set up in conjunction with Duke University ECG core lab in 2002 to examine the issues of Magnetic And eLectrical Technologies (MALT). Some of the initial findings are presented here. The priority issue that has been uncovered is that images produced using ceMRI to determine infarct size will have to undergo a rigorous process of validation to ensure global agreement regarding the image acquisition and post processing. A similar situation that automated ECG analysis was at 30 years ago and addressed by the Common Standards for quantitative Electrocardiography (CSE) (117). Ultimately, rather than validation of ECG scoring systems, the role of ceMRI will be to revise ECG criteria.

### 3.4 Cardiac biomarkers in acute myocardial infarction

This section describes the evolution of biomarkers in assessment of myocardial infarct size from CK, CK-MB to TnI and previous studies using ceMRI are highlighted. The role of CRP in AMI is discussed and the potential contribution of ceMRI suggested.

#### **Creatine kinase**

Serum biomarkers were the first in vivo measures of infarct size and developed once it was realised that the evolution of myocardial infarction was dynamic and could be modified. The first to be used was creatine kinase (CK) and specificity was improved by measurement of the MB fraction (CK-MB). The release characteristics of these biomarkers were then studied to determine the optimal sampling time and frequency using a gold standard for infarct size. These gold standards lacked precision and included the ECG, LV ejection fraction, haemodynamics, arrhythmias and prognosis. In animal studies it was possible to make direct measurements at autopsy. Sampling methods used were total enzyme released, peak levels and area under the curve. This intensity is possible in animal studies and clinical trials but translation into clinical practice is difficult because of the time delays intrinsic to each patient's presentation and the impracticalities of frequent sampling.

It was noted that the kinetics of release were altered by reperfusion. A greater peak and more rapid decline makes comparison of reperfused with non-reperfused infarcts problematic. Regardless of formal reperfusion status; there will be differences in many other aspects including spontaneous occlusion and reperfusion, subtotal occlusions, collateral flow, infarct haemorrhage, oedema and degree of ischaemic preconditioning.

## **Troponin**

Troponins (T or I) are very sensitive markers for the detection of myocyte necrosis and therefore AMI. With the publication of the ACC/ ESC guidelines in 2000, troponin measurement became central to the redefinition of myocardial infarction with less emphasis on corroborative evidence from the history and ECG (118;119). The measurement of serum troponin is now part of routine clinical practice in the diagnosis of patients with symptoms suggesting ACS. However, the infarction is in progress by the time the current routine biomarkers are detectable in venous blood and the non cardiac causes for troponin release are well documented. These include acute myocarditis and cardiomyopathies such as Takotsubo, pulmonary embolism, chronic renal failure and sepsis (120). Total troponin released would be the ideal marker for infarct size but is impractical as it remains elevated for up to 2 weeks, so fixed time points have been explored. There is an excellent correlation between troponin and infarct size by ceMRI and SPECT at 72 and 96 hours (15;16). The clinical reality is that patients will get a single troponin checked at between 8 and 12 hours enabling early risk stratification, for example to determine suitability for inpatient coronary angiography. It would therefore be more clinically relevant to study the association with infarct size at this single time point.

Cardiac biomarkers are sensitive in the detection of acute myocardial necrosis but are not necessarily specific to ischaemic aetiology. Patients who are troponin positive have been observed to have minimal coronary artery disease at angiography (121-123). There is debate whether this represents a “false positive” and speculation as to the potential coronary causes such as spasm or embolus. These patients have been shown to be at increased risk of death or MI, although the mechanism underlying this adverse outcome is unclear (124). The more likely

explanation is that troponin is not “false positive” for myocardial necrosis, rather not as specific for the aetiology of necrosis as was first thought.

Since this study was initiated, both peak CK and troponin have been tested against ceMRI for assessment of infarct size (125). There is generally a good correlation with these biomarkers and reperfused infarcts. The correlation in non-reperfused infarcts is not as strong and in some cases does not reach significance. The additional information that will be provided in this study is the assessment of the clinically used troponin sampling point in those patients with single acute MI. The study population includes patients admitted with chest pain syndrome so additional information on the aetiology of troponin release was investigated. CeMRI can also detect episodes of previous myocardial damage that would be outwith the biomarker radar. In those patients with chest pain but a normal troponin ceMRI will provide information on previous “silent” ischaemic or non-ischaemic damage.

### **C reactive protein**

Early in the atherogenesis process there is involvement of inflammatory cells such as leucocytes in response to triggers such as infection, injury and oxidised lipids. The migration of these inflammatory cells into the subendothelial space is induced by several adhesion molecules. Thus begins the formation of foam cells, fatty streaks and the atheromatous lesion with fibrous cap. Local smooth muscle cells in the artery wall continue to promote inflammation by triggering the release of cytokines (particularly IL-6), chemokines and growth factors. These have a local regulatory role but also induce the production of liver derived acute phase proteins such as CRP. CRP may then itself play an active role in atherogenesis by mediating LDL uptake by macrophages, stimulating monocyte release of cytokines,

modulating monocyte chemotactic protein-1 induction in endothelial cells and exerting a direct effect on endothelial cells to express adhesion molecules (126-129). CRP is the most widely studied marker of inflammation and has been shown to provide independent prediction of cardiovascular risk for both primary and secondary prevention (130-133).

CRP is also implicated in the ultimate stage of coronary atherosclerosis that is myocardial infarction. It has been shown to be elevated within 6 hours of onset of AMI and peaks at 50 hours (134;135). A CRP measurement will provide information on cardiovascular risk (death, MI) early post MI (133;136), at 6 months using a cut off of 10mg/L (137) and at 5 years (138). In each of these studies CRP provided additive information to serum troponin.

The exact source for CRP in ACS remains unclear and it seems likely that plaque rupture and myocyte necrosis are the main contributors. A CRP >3 mg/L is associated with a plaque rupture lesion and <3 mg/L with a plaque erosion lesion (139). In unstable angina an intracardiac inflammatory process appears to be the result of myocyte necrosis (140). CRP has been associated with infarct size when estimated using CK, CKMB and SPECT (141). An elevated CRP has been shown to predict infarct expansion and cardiac rupture in patients with their first Q wave myocardial infarction (136). Some models of reperfusion injury suggest that neutrophil accumulation plays a key role and in animal studies leukocyte depletion leads to a reduction in the no reflow phenomenon (142;143). More evidence is emerging that implicates CRP in MVO due to its effects on endothelial function, cell adhesiveness and cytokine release (144-146). In a rat model Griselli et al. demonstrated that injection of human CRP is associated with increased infarct size (147).

### **3.5 Matrix metalloproteinase-1 and left ventricular remodelling post acute myocardial infarction**

Matrix metalloproteinases (MMPs) are a family of enzymes responsible for the degradation of the extracellular matrix. Several MMPs are expressed in human myocardium and play an important role in left ventricular (LV) remodelling after AMI (148;149). The principal structural protein in the human myocardium is type I collagen, with a lesser contribution from type III collagen (150). These fibrillar collagens can be degraded only by MMP-1 and membrane-type MMP-1, suggesting that these enzymes must play a pivotal role in LV remodelling. Supportive evidence for the importance of MMP-1 in this process comes from animal models and from human studies demonstrating increased myocardial enzyme and messenger ribonucleic acid expression and elevated circulating levels after AMI (150-155).

MMPs are regulated at 3 levels: gene transcription, the activation of latent enzymes, and inhibition by tissue inhibitors of metalloproteinases (148;156). For most MMPs (with the exception of MMP-2), transcription is the key regulatory step (156). This in turn is influenced by promoter sequences that exhibit deoxyribonucleic acid polymorphisms, some of which exert allele-specific effects on gene transcription. Functionally significant polymorphisms have been identified in the promoter sequence of MMP-1. Specifically, a guanine (G) addition, creating a GG allele, increases enzyme production (156;157). It was hypothesised that patients with the GG allele might be predisposed to increased remodelling after AMI.

## 3.6 Aims

### **Bioelectrical markers**

To demonstrate that on the presenting ECG, the currently accepted GUSTO and ACC/ESC ST segment elevation criteria have high specificity but low sensitivity for the diagnosis of acute myocardial infarcts

To investigate the diagnostic benefits of considering STEMI-equivalent ST-segment depression criteria.

### **Biochemical markers**

To determine the incidence and extent of infarcts meeting ACC/ESC biochemical marker, i.e. troponin positive, criteria that are not detected by ceMRI and so define minimal myocyte necrosis.

To describe the ceMRI findings in patients with positive troponin but negative coronary angiography.

To assess the diagnostic ability of CRP in acute chest pain syndromes both linearly and using a cut off of 10 mg/L.

To assess the correlation between CRP and infarct size by ceMRI in both reperfused and non-reperfused infarcts.



## **Infarct size**

To compare infarct size by CK, CKMB, TnI and Selvester score with ceMRI and to assess the relationship between the Selvester score, TnI and ceMRI as measures of acute reperfused and non-reperfused infarct size.

To investigate if there is an improved correlation with these same markers and final infarct size by ceMRI at a mean of 38 days.

To investigate whether the combination of Selvester scores added to TnI will improve the correlation with acute infarct size by ceMRI.

To document the change and rate of change in infarct size over a 1 year period by imaging at the routinely used follow up time points of 28 days, 6 months and 1 year.

## **MVO**

To define early and late MVO and their incidences.

To document the change and rate of change in early and late MVO and to examine their role in infarct healing.

To assess the sensitivity and specificity of CRP in its ability to identify both early and late microvascular obstruction using the pre-specified cut off points of 3 and 10 mg/L and define a new cut off for the detection of early and late MVO.

## **LV remodelling**

To document change and rate of change of LV dimensions over 1 year using the above time points.

To assess the relationship between matrix metalloproteinase-1 promoter genotypes and remodelling in patients after their first acute myocardial infarction.

### **Additional findings**

To describe those findings by ceMRI seen in patients presenting with their first episode of ischaemic chest pain without the 'sine qua non' diagnosis of single AMI. The initial and follow up findings for the 63% of patients who do not have single AMI by strict biomarker, ECG and ceMRI criteria are described.

To document the incidence of common complications of AMI such as RV infarction and LV thrombus and compare the diagnostic capabilities with standard practice.

## 4 Methods

### 4.1 Patient recruitment

One thousand two hundred and seventy eight consecutive patients admitted to the Western Infirmary, Glasgow with symptoms suggesting an ACS between August 2002 and May 2003 were screened for this study. This hospital is the primary medical centre for a population of 300 000 located in a metropolitan area in a surrounding mixed suburban/rural region in Western Scotland. For each patient there was an initial case note review performed the morning after admission to assess suitability for the study. Basic demographic data including diagnosis and reason for exclusion were recorded. Patients were excluded if they: had a past medical history of angina; had significant comorbidity; were unable or refused to consent for the study; were transferred from another hospital; or had contraindications to ceMRI (ferrous implants, severe claustrophobia, pregnancy and unable to remain supine for  $\geq 45$  min). Patients that met the inclusion criteria were then interviewed, the study discussed and approved information sheet distributed **Information sheet for patients/ volunteers in clinical research project, 12.2 below**. Once consent was obtained patients were asked to complete a patient information questionnaire **Personal Health Record, 12.3 below** and were listed for the next available ceMRI slot.

The study of the remaining 153 patients complies with the declaration of Helsinki . The West Ethics committee of North Glasgow University Hospitals Trust approved the protocol for the study and all participants gave their written informed consent (R&D reference no: 02 CA012VRW).

The aim for this study was to scan patients as soon as practically possible following chest pain onset. After clinical stabilisation 153 patients were studied with ceMRI at mean (SD) 55 (32) hours. Delays included weekends and the clinical protocol mandated 48 hours in CCU for all STEMI patients. The study did not interfere with routine clinical care and the primary means of restoring coronary artery patency at the time of the study was intravenous thrombolysis.

Information gathered in conjunction with routine clinical practice was at the following time points: in Accident in Emergency (presentation), 8-12 hours after chest pain and at the time of each ceMRI scan. Data collected included: additional blood sampling for troponin (including dilutional analysis), CK/ CKMB, CRP and ECG recording. The results of the ceMRI scan were made available to the clinician in charge of the patients care in the form of a subjective report. Final discharge diagnosis as presented in this study was determined by the clinical judgment of the physician in charge of the patient's care. Infarct acuteness was defined by a rise and fall of TnI ( $>0.02\text{ng/ml}$ ) during 3 serial measurements, absence of ECG evidence of prior MI and the presence of single region of DE at ceMRI.

At each visit, all patients underwent a clinical evaluation, ceMRI, ECG and blood testing.

The planned study schedule and follow up was based on the initial ceMRI scan and three follow up visits at 28 days, 6 months and 1 year.

1. **During initial hospital admission** number= 153, at mean (SD) 2.28 (1.3) days
2. **28 days** n= 122, at 39 (17) days
3. **6 months** n= 105, at 205 (34) days
4. **1 year** n = 80, at 389 (46) days

The study design complies with the Declaration of Helsinki. The Ethics Committee of the North Glasgow University Hospitals NHS Trust approved the protocol for study. All participants gave their written informed consent.

## 4.2 Specific study inclusion/ exclusion criteria

For the studies of ST deviation on admission ECG, myocardial infarction size and characteristics by ceMRI, further exclusion criteria were applied to the 153 patients determined by each research question. Specific study criteria are outlined below.

### **ST-segment deviation analysis of the admission 12-Lead ECG as an aid to early diagnosis of AMI with a ceMRI gold standard**

Thirty-five patients (23%) were excluded from this study because of confounding factors in the admission ECG. These ECG factors include diagnostic evidence of prior AMI (n = 17); left ventricular (LV) hypertrophy (n = 9); atrial fibrillation with high ventricular rate (n = 1); Wolff- Parkinson-White syndrome (n = 1); bundle branch block (n = 5); right ventricular hypertrophy (n = 1); and excessive artifacts (n = 1). The study was of the remaining 116 patients. The diagnosis of STEMI for the final analysis was made according to the stated criteria on the basis of the findings of the ECG core lab. The diagnosis of NSTEMI included all those patients with evidence of myocardial infarction as defined by the presence of DE rather than by biomarkers alone. All STEMI and NSTEMI patients, except 4, had positive biomarkers and a rise and fall over three separate time points (admission, 12 h, and at the time of ceMRI). Of the 4 with negative biomarkers (false positive by ceMRI for AMI), 3 did not have ST segment deviation on the admission ECG. The 4th patient met the STEMI-equivalent criteria (ST-segment depression had resolved on the repeat ECG the following day) and had a diffuse pattern of DE associated with an inferior and posterolateral hypokinetic regional wall motion abnormality. Coronary angiography was not performed in this patient.

## **Validation of electrocardiographic and biochemical estimates of first MI size using ceMRI**

Eighty (52%) patients had acute myocardial necrosis by a rise and fall of TnI. Four were excluded on the basis of ECG evidence of prior MI. Myocardial infarction was defined as the presence of DE in a subendocardial distribution and in a single coronary artery territory (LAD, LCx or RCA) by the AHA 17 segment model (70). Once ceMRI was performed there had to be a single infarct location only, if greater than one then one of the infarcts was assumed to be old. Nineteen patients were excluded from this study population based on their ceMRI findings. Seven patients had evidence of myocardial infarction in greater than one separate coronary artery territories (six with at least anterior involvement), four patients had subendocardial sparing as the pattern of hyperenhancement in keeping with non ischaemic fibrosis and eight patients had no evidence of hyperenhancement and therefore labeled as minimal myocyte necrosis.

The study was of the remaining 57 patients, 31 (54%) of whom received IV thrombolysis (STEMI). Patients were assessed for reperfusion at 90 minutes by repeat ECG. In 6 patients there was ongoing chest pain and less than 50% ST resolution so rescue PCI was performed. The 26 (46%) patients with diagnosis of NSTEMI were managed conservatively on the acute medical ward until biomarkers available at 8-12 hours.

## **Serial assessment of myocardial infarction size and characteristics using ceMRI**

Patients with single AMI, as defined above, were included in the analysis for this study and information from all four time points included in the analysis.

### **Usefulness of CRP in detecting higher risk patterns of MI defined by ceMRI**

Subgroup analysis was performed in 2 groups. The first was defined by ceMRI and consisted of the 57 patients who had acute myocardial ischaemia as above. These patients were used in the assessment of the correlation of CRP with acute and final infarct size and LV remodelling by reperfusion status. In the second group the sensitivity and specificity of CRP in the detection of microvascular obstruction was tested in the 80 patients that were troponin positive.

### **Matrix Metalloproteinase-1 Promoter Polymorphisms and Changes in Left Ventricular Volume Following Acute Myocardial Infarction**

Of the 68 patients with acute MI (TnI positive and subendocardial DE), 42 underwent further study to investigate MMP-1 promoter polymorphisms in LV remodelling. The reason for exclusion of 26 samples was that they were unsuitable or insufficient for this analysis.

### **Additional ceMRI findings in patients with first hospital admission to rule out MI**

Fifty seven (37%) patients had the expected first presentation with single AMI defined by patient history, ECG, biomarkers and ceMRI. The ceMRI findings of the remaining 96 patients, “non” single AMI, are described according to the following groups: minimal myocyte necrosis; chest pain, other; unstable angina; acute myocarditis; prior myocardial infarction; acute and prior myocardial infarction; prior non-ischaemic fibrosis, **Figure 5-4**.



### 4.3 Contrast enhanced Cardiac Magnetic Resonance Imaging

Cardiac and blood pressure monitoring using the Schiller (Schiller AG, Baar, Switzerland) monitoring equipment provided a continuous ECG trace and regular blood pressure recording similar to the level of monitoring in CCU. Every scan was supervised by at least one member of the medical staff experienced in Cardiology. CeMRI was performed on a 1.5-T whole-body scanner (Siemens Sonata, Erlangen, Germany) with a phased-array chest coil as the receiver during breath hold and gated to the ECG.

Table 4-1: Preparation of patient for ceMRI

1. Prepare
a. Syringe A: Gadolinium (Gd)-DTPA (Omniscan, Nycomed) dose = 0.2 mmol/kg
b. Syringe B: 0.9% NaCl solution as flush
2. Enter patient data in scanner
3. Place patient on table
4. Attach Siemens active Brooker ECG electrodes
5. Lead selection for optimal positive R-wave configuration
6. Insertion of 20 G I.V. catheter in antecubital vein. Flush with 10 ml 0.9% NaCl solution
7. Place and align phased array chest coil (Siemens CP body array flex)
8. Patient enters scanner

## **CeMRI image acquisition**

### ***(i) LV structure and function***

#### *1) Scout images*

Once the patient in the scanner a multi-slice breath-hold localiser scan was used.

Protocol: Multi-slice single-shot breath-hold steady-state free precession (SSFP) or TrueFISP (Siemens) localiser with transversal, sagittal and coronal slices. Field of view (FoV) = 360 mm, FoV phase = 81.3%, slice thickness = 6 mm, repetition time (TR) = 3.41 ms, echo time (TE) = 1.71 ms, flip angle (FA) = 60°, averages = 1, measurements = 1, phase resolution = 80, phase oversampling = 0%.

#### *2) Localiser images*

The best axial image that depicted the left ventricle and septum was used to plan 3 vertical long axis (LA) localisers along the long axis of the LV from the mid-point of the mitral valve to the apex.

From the resulting vertical LA scan, 3 horizontal LA localisers were planned, again using the mid-point of the mitral valve and the apex of the left ventricle to prescribe the orientation.

From the 3 horizontal LA slices produced, 3 SA localiser slices with orientation parallel to the mitral valve plane using the anatomical landmark of the atrio-ventricular groove were planned.

The basal slice was positioned into the atria to depict the LV outflow.

From the resulting SA images, three LA views were planned: the four-chamber (4CH); two-chamber (2CH); and LV out-flow tract (LVOT). Cinematographic (CINE) studies were then obtained.

SSFP CINE protocol: TrueFISP breath-hold CINE. FoV=340 mm, FoV phase=81.3%, Slice thickness=8 mm, TR=47.4 ms, TE=1.58 ms, averages=1, FA=60°, measurements=1, phase resolution=65%, phase oversampling=20%, segments=15.

### 3) *Short axis CINE stack*

From the 4CH CINE, the SA CINE stack encompassing the entire left ventricle was planned. The first of these SA CINE slices was planned in an orientation across the mitral valve plane, again using the atrio-ventricular groove as an anatomical land-mark. The end-diastolic image from the 4CH CINE study was used to plan the first and most basal SA slice.

The slice position was then incremented by 10 mm moving towards the apex region of the left ventricle and repeated until the left ventricle has been completely covered thus inter-slice gaps of 2 mm were used.

### **(ii) Contrast enhanced cardiac MR imaging**

Contrast dose, time between injection of the contrast agent to image acquisition are important for accurate DE visualization and these were kept constant(158). Following SA image acquisition a single dose of 0.2mmol/kg Gd- DTPA-BMA (GE Healthcare, Waukesha, Wisconsin) was injected via an antecubital vein. CeMRI was performed with the single shot (159) and standard segmented gradient-echo inversion-recovery sequences (33;48;58).

### 1) *Early MVO imaging*

Image acquisition using the “single shot” inversion recovery SSFP was started 2 minutes following contrast injection using the same slice positions as for all SA CINE slices. No breath holding is necessary and imaging in a single heart beat is possible **Figure 6-1**.

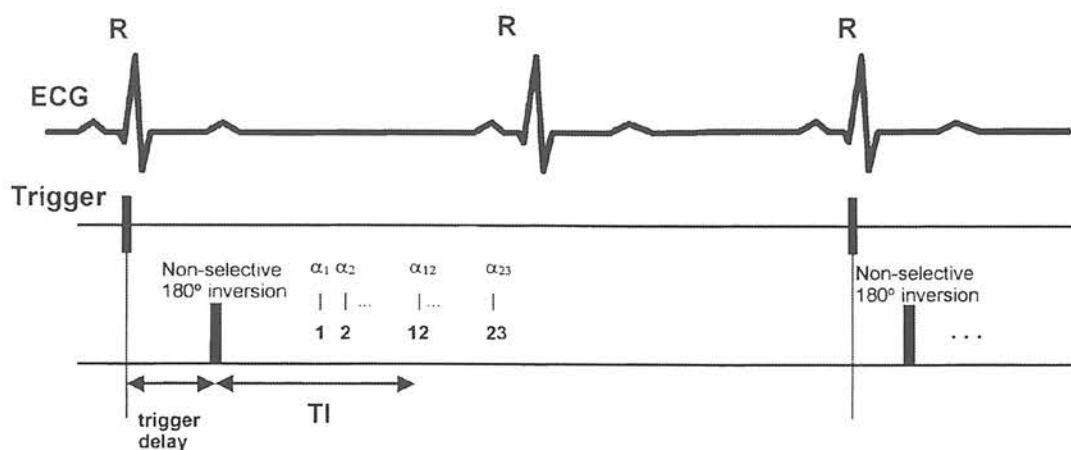
Protocol: ECG trigger, 100 lines field of view =270 x 360, slice thickness =8 mm, interslice gap = 2 mm, flip angle 30 degrees, TE 1.2 ms, TR 2.7ms, TI 200-350ms, bandwidth/ pixel 980 Hz, matrix 256.

## 2) *Delayed hyper-enhancement Gd-DTPA imaging (DE)*

Image acquisition using the inversion recovery fast gradient echo sequence was started 10 minutes post Gd-DTPA injection to allow time for necessary adjustments before start of actual image acquisition at time = 15 minutes. Identical slice positions to SA CINE and early MVO images were used starting at the mitral valve plane as before. LVOT, 2CH- and 4CH LA slices were also acquired.

Protocol: Breath-hold segmented rephased Turbo Flash (Siemens) sequence with non-selective inversion pulse with non-slice selective inversion-recovery **Figure 4-1**.

Constants: FoV=340 mm, FoV phase=81.3%, slice-thickness=8 mm, inter-slice gap=2mm, TE=4.3 ms, averages=2, flip-angle=30, phase-resolution=65%, segments=25, trigger delay=0, trigger pulse= 2 but dependent on scan time (1 if bradycardic, >2 if tachycardic) to allow for sufficient longitudinal relaxation between inversion pulses.



**Figure 4-1: Segmented inversion-recovery turboFLASH sequence with TI set to null normal myocardium after contrast agent administration**

Variables: The acquisition window was set greater than RR-interval and TR just under to allow for diastolic imaging. Inversion time (TI) was 250 ms (for initial scan) and adjusted according to image quality by 10 ms steps to optimise image quality. Optimum TI and TR produced a diastolic image with black (nulled) myocardium and bright late enhancement area. Blood appeared with an intermediate intensity **Figure 6-2**.

### **Guide to adjustments used to improve image quality:**

TI too short: infarct nulled and normal myocardium bright white;

TI too long: infarct may be white but normal myocardium grey (rather than black);

TI close; infarct white, myocardium speckled change the TI by just 10 ms to attain optimal suppression of myocardium.

Dark signal at the endocardial boundary: the effective T1 of the tissue at the blood-myocardial interface is often slightly shorter, due to mixing. This indicates that the inversion time is too short. Therefore, increase TI to obtain uniform suppression of the myocardium.

Blood pool too dark: TI is too short, increase TI.

Blood pool too bright: TI is too long, decrease TI.

In order to decrease the dependence of optimal TI when acquiring DE-MRI images a phase sensitive acquisition technique was used (90).

### **CeMRI Image Analysis**

A blind, random ordered analysis of all ceMRI examinations was undertaken by one observer in as few batches as possible once the study was completed. Image analysis was performed using Siemens Argus software for LV mass and function and CMR tools (Imperial College, London) for manual DE area planimetry.

#### ***(i) Left ventricular structure and function analysis***

Measurement of LV mass and function was evaluated with manual planimetry on commercially available Argus software (Siemens, Erlangen). In each examination, the number of slices to be included in the covering of the left ventricle in end-diastole and end-systole were decided. End-systole was chosen at the point where the LV blood pool is smallest. On each end-diastolic and end-systolic frame, both endocardial and epicardial circumferences of the LV myocardium were manually planimtered and the corresponding areas calculated. The papillary muscles were included as part of the LV myocardium. Total volumes of the left ventricle were then calculated by simple addition of the individual SA slice areas in the stack slices covering

the left ventricle. In this manner, LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes (ml) were determined and LV ejection fraction (LVEF, %) and LV myocardial mass (LVM, g) calculated. The latter calculation assumes a myocardial density factor of 1.05 g/ml.

### ***(ii) Delayed hyperenhancement (DE) analysis***

The ceMRI data were analysed with CMR Tools (Imperial College, London). There are a variety of commercially available post processing software programmes used to measure infarct size and even the simple choice of whether whole pixels are located within, on or outwith the perimeter varies between different software. The same software for all DE analysis was used.

The high accuracy of the ceMRI technique for depicting areas of infarction shown in animal studies relies on quantification of hyperenhanced areas in high spatial resolution (0.5 x 0.5 x 0.5 mm) ex vivo images. This high spatial resolution is not obtained when acquiring standard ceMRI images in routine clinical practice. The typical spatial resolution of a clinically acquired ceMRI image is 1.5 x 1.5 x 8 mm. Thus, the thickness of standard infarct MR images is 16 times that of the high spatial resolution MR image acquired ex vivo. Consequently, the problem of partial volume arises in the clinical setting (33). Within the 8 mm thick image slice the infarcted myocardium can be very irregular, resulting in blunted infarct borders. In order to maintain objective consistency no allowance for partial volume was made in this study i.e. anything that was hyperenhanced was included.

Relative contrast and brightness varies with different image display systems and can be manually altered to optimise visualisation of the infarcted myocardium. By doing so, the periphery of the hyperenhanced region is manipulated subjectively, which can affect the

assessment of MI size in an unpredictable manner. In this study no manual adjustments to the image were used – planimetry was performed on the image as presented by the software, no “windowing” **Figure 6-2** and **Figure 6-3**.

The signal intensities of Gd-enhanced myocardium and normal myocardium were measured with computer-assisted planimetry and delineated manually. Delayed hyperenhancement that involves the subendocardial area was considered to represent an MI scar (72;160).

Subendocardial sparing was identified visually and defined as DE that did not at any point extend to the subendocardium i.e. nulled myocardium was visible between the blood pool and region of DE on both long and short axes (72). The best quality images from the SA stack that contained DE were selected for analysis and for each SA slice the DE area was planimetered. A myocardial volume was calculated by the sum of each area. Infarct mass then calculated by multiplying the volume by a factor of 1.05 g/ml as above.

All DE images from the admission ceMRI scan were analysed twice to measure intra observer variability calculated as part of quality control. The mean value of both images was used in the final analysis. All screenshots of DE planimetry were saved and one in five images were qualitatively assessed by a second observer (BAG).

### ***(iii) Infarct characteristics***

#### ***1) AMI location***

The AMI location was determined by the 17 segment AHA standardised myocardial segmentation model(70) into anterior, lateral and inferior. The location was defined as the region of the LV containing the highest percent infarction; patients were classified as having multiple infarcts if there were >1 separate areas of DE. In some cases it was not possible to



assign an infarct to one particular territory so a hybrid was used e.g. inferior and lateral **Figure 6-4**.

### *2) Microvascular obstruction*

Microvascular obstruction (MVO) was considered present when at least one segment had a central core of hypoenhancement surrounded by hyperenhancement (161;162). Early MVO is seen between 1 and 5 minutes post contrast (87) and late (persistent) MVO when the appearance persists for  $\geq 10$  minutes(67). The region of hypoenhancement was manually planimetered as for DE images **Figure 6-5**.

### *3) Infarct transmural*

Mean transmural (TM) score was calculated by visually deciding the transmural extent per segment in quarters (1 - 1-25%, 2 - 26-50%, 3 - 51-75%, 4 - 76-100%) and calculating the mean. A myocardial infarct was labeled TM of mean score  $\geq 3$  (48). **Figure 6-4**, left and right panels show an anterior and a lateral infarct both with mean TM score of  $\geq 3$ , the middle panel shows an inferior infarct with a mean TM score  $\leq 3$ .

### *4) Endocardial extent of infarct*

Endocardial extent was calculated by measuring the circumferential extent of the infarct at each of the SA slice used in the AHA segmentation model (70) and the mean value used in the analysis **Figure 6-6**.

## 4.4 12 lead Electrocardiography

All ECGs were quantitatively and qualitatively evaluated in the Duke University Medical centre ECG core laboratory (North Carolina, USA) by 2 investigators (GW, RS), who were blinded to all other study data. An ECG for analysis was recorded at presentation, at 8-12 hours and at the time of each ceMRI scan.

The ST-segment measurements were made at the J point to the nearest 0.05 mV, and all differences were adjudicated in conference. Regarding “contiguity,” the 6 chest leads and the spatially based orderly sequence of the 6 standard limb leads were considered (163).

The ECGs were classified according to the following 3 criteria:

1. GUSTO STEMI:  $\geq 0.1$  mV ST-segment elevation in  $\geq 2$  anatomically contiguous standard limb leads (among I, II, III, aVL, and aVF) or  $\geq 0.2$  mV in  $\geq 2$  contiguous standard precordial leads (94).
2. ACC/ESC STEMI:  $\geq 0.1$  mV ST-segment elevation in  $\geq 2$  anatomically contiguous standard limb leads (in their orderly sequence from aVL to III, including -aVR) or chest leads V4 to V6, or  $\geq 0.2$  mV in chest leads V1 to V3 (164).
3. STEMI equivalent:  $\geq 0.1$  mV ST-segment depression in  $\geq 2$  anatomically contiguous leads or in 1 lead that is anatomically contiguous to a lead with ST-segment elevation criteria (e.g., ST-segment elevation in lead aVL and ST-segment depression in lead III and vice versa).

At the time of study recruitment acute reperfusion was based on the GUSTO set of criteria so this is the definition of STEMI for analysis i.e. the terms STEMI and “reperfused infarct” are

synonymous. The exception is the study entitled, “ST-Segment deviation analysis of the admission 12-Lead ECG as an aid to early diagnosis of AMI with a ceMRI gold standard”.

Patients defined as ST deviation were those with with either ST elevation or depression. “No ST deviation” includes those patients in whom nether of the above criteria were met.

The complete 50-criteria, 31 point Selvester QRS scoring system (165) adapted from the original 54 criteria 32 point system(110) was performed contemporaneously with each ceMRI scan **Selvester Score** page 197.

Pathological Q waves were defined as negative deflection in the first part of QRS complex of  $\geq 1$  mm deep and  $\geq 2$  mm wide in at least 2 contiguous leads. T wave inversion considered significant if  $\geq 2$ mm below baseline.

## 4.5 Biomarkers

### Sample timing

Troponin I and CK/ CKMB: at presentation, 8-12 hours post chest pain onset as per clinical protocol, at the time of ceMRI scan 1.

CRP: at the time of ceMRI scan 1.

Renal function and full blood count: at presentation, 8-12 hours post chest pain onset as per clinical protocol, at the time of ceMRI scan 1.

### Assays

Troponin: Bayer Advia Centaur Immunoassay analyser (Bayer, Tarrytown, New York) which has a coefficient of 18% at the reference limit of 0.2 ng/ml and a 99<sup>th</sup> percentile for normal controls of 0.16ng/ml(166).

CK: Bayer Advia 1650 Random Access Analyser- colorimetric assay.

CK-MB: Bayer Advia Centaur Immunoassay analyser

CRP: Ultra sensitive double antibody sandwich ELISA (linear up to 5mg/L and logarithmic thereafter). The inter-assay coefficient of variation was less than 7% across the range of measured results.

NtBNP: Roche diagnostics chemiluminescent kit on an Elecsys 2010 analyser. The coefficient of variation is < 5%

## 4.6 Matrix metalloproteinase-1 promoter polymorphisms

Deoxyribonucleic acid samples were prepared from whole blood using a commercially available extraction kit (Tepnel Life Sciences PLC, Wythenshawe, United Kingdom). Polymerase chain reaction was used to amplify a region across the G insertion in position -1607, consisting of 317 or 318 base pairs (bp), depending on the presence or absence of the insertion. The sense primer for this amplification flanks the polymorphism at the site -1823 to -1802 bp (5'-CCCTCTAATATGAAGAGCCCC-3') and the antisense primer at -1506 to -1526 bp (5'-TTCCTC-CCCTTATGGATTCC-3'). The polymerase chain reaction conditions were 35 cycles of 30 seconds at 94°C, 30 seconds at 59°C, and 30 seconds at 72°C. A second nested mutagenesis polymerase chain reaction of this amplified sequence was then undertaken to create a GGATCC restriction site for the enzyme BamHI when adjacent to the GG polymorphism: sense 5'-GCTGGAGTCACTTCAGTGGC-3', antisense 5'-TATCTTGGATTGATTTGAGATAAGTCGGAT-3', 35 cycles of 30 seconds at 94°C, 30 seconds at 60°C, and 30 seconds at 72°C. These polymerase chain reaction products were then digested with BamHI and the products (defining genotype) separated by gel electrophoresis and visualised by ethidium bromide staining. All polymerase chain reaction reactions included negative controls, without deoxyribonucleic acid template, to exclude the amplification of contaminants. Repeat polymerase chain reaction of 20% of the samples confirmed consistent results. Patients were grouped according to their genotypes.

Blood samples were transferred to the Department of Cardiology, Aberdeen Royal Infirmary where all further sampling including PCR was undertaken as part of a collaboration with Dr. Graham Hillis (see acknowledgements).

## 4.7 Coronary Angiography

Diagnostic coronary angiography and follow on percutaneous intervention was performed during admission at the discretion of the Cardiologist performing the procedure in the Western Infirmary.

Qualitative analysis was performed by at least one experienced operator independent from this study. Significant stenosis is defined as  $\geq 70\%$  luminal narrowing, moderate disease as 50-70%, mild disease as 25-50% and classified as normal if  $<25\%$  or plaque disease.

## 4.8 Statistics

Statistical analyses were performed with SPSS for Windows (version 14. 2005. Chicago, Illinois, USA).

Baseline demographic data and clinical characteristics for patient groups as stated in results section were compared with the 2-sample t test (or Wilcoxon rank sum test for skewed measurements) for continuous variables and the chi-square test for categorical variables (or Fisher Exact test if expected counts  $\leq 5$ ). Graphical procedures and the relation of the standard deviation (SD) to the mean were used to check whether the data were normally distributed. In each case the value for the SD was either greater or close to the mean value. Exact p values are reported where possible and the level of significance was set at  $p \leq 0.05$ . Summary statistics are presented as mean (SD) or median (IQR) for continuous variables and number (%) for categorical variables. Analysis of variance using paired samples was used to compare change in infarct size with time and to compare the difference in change in infarct size between subgroups.

The sensitivities and specificities of the GUSTO STEMI, ACC/ESC STEMI, and STEMI-equivalent criteria were compared with the ceMRI gold standard using the McNemar test. The 95% confidence intervals (CI) were calculated for each statistic from the binomial distribution.

Correlation was assessed by Spearman rank correlation coefficient for non parametric data. Multiple linear regression using ceMRI as the dependent variable and TnI then TnI plus Selvester score as fixed factors was used to assess any improvement in the correlation with

infarct size using the combination. For the multiple linear regression the Pearson correlation coefficient was used.

Receiver operator curves (ROC) were used to assess diagnostic ability of CRP and to determine optimal levels for the detection of early and late MVO in the troponin positive patients. The sensitivities and specificities of the predefined cut offs of 3 and 10 mg/L and the ROC curve determined optimal cut off were compared to the ceMRI gold standard using the McNemar test. The 95% confidence intervals (CI) were calculated for each statistic from the binomial distribution.

For MMP-1 and LV remodelling, it was prospectively defined that patients would be dichotomised and genotype frequencies compared on the basis of a  $\leq 10\%$  or  $> 10\%$  increase in LV volumes. It was estimated that to detect a 10-ml difference in LV volume, with a SD in measurement of 10 ml at a 2-sided significance value of 0.05 and 80% power, a sample size of 32 patients would be required, assuming approximately equal frequency of the 2 alleles. Genotype distributions were consistent with Hardy-Weinberg equilibrium.

All ceMRI scans from visit 1 were assessed twice by the same observer and the coefficient of variation calculated to be 3.4%.

The Z test was used to compare 2 independent correlations when testing the improvements of Selvester score and TnI with final infarct size and final LVEF.



## 4.9 Definitions

### Cardiovascular risk factors

Smoking: >10 pack years of tobacco use. Family history:  $\geq 2$  first degree relatives with a history of premature cardiovascular disease ( $\leq 60$  years). Hypertension: treated hypertension prior to hospital admission. Hypercholesterolaemia: lipid lowering therapy initiated prior to admission. Diabetes: grouped together as type I and type II requiring medical (oral and insulin) therapy.

MACE (major adverse cardiovascular event) was defined as death, MI, emergency revascularisation, hospital admission with heart failure or stroke. Patients were followed up by case note review at 3 years. MACE was not a primary end point of this study.

### Definitions of Primary Discharge Diagnosis

Final diagnosis is reached by a combination of clinical and ceMRI findings **Figure 5-4**.

#### ***(i) Single Acute Myocardial Infarction***

Patients that had a rise and fall of troponin over three sample points, no evidence of prior MI by ECG and subendocardial DE in single coronary artery territory.

#### ***(ii) Prior myocardial infarction***

Patients that were TnI negative and subendocardial DE positive.

#### ***(iii) Acute and prior myocardial infarction***

Patients that were TnI positive and had >1 region of subendocardial DE.

#### ***(iv) Prior non-ischaemic fibrosis***

Patients that were TnI negative with subendocardial sparing of DE.

**(v) *Acute myocarditis***

Patients that were TnI positive with subendocardial sparing of DE.

**(vi) *Unstable angina***

Patients that were TnI and DE negative but had ST deviation/ significant T wave inversion on the ECG and/ or significant coronary angiographic findings (>70% stenosis), including coronary artery spasm. A positive exercise tolerance test is included if no subsequent coronary angiography performed.

**(vii) *Chest pain, other***

Patients that were TnI and DE negative for whom either an alternative diagnosis was made or there was no further objective evidence for ischaemic heart disease. There are 5 patients in this group who were labeled “unstable angina” without objective evidence and started on anti-ischaemic drug therapy. The clinical diagnosis of pericarditis was made in 2 patients with typical history and ECG findings.

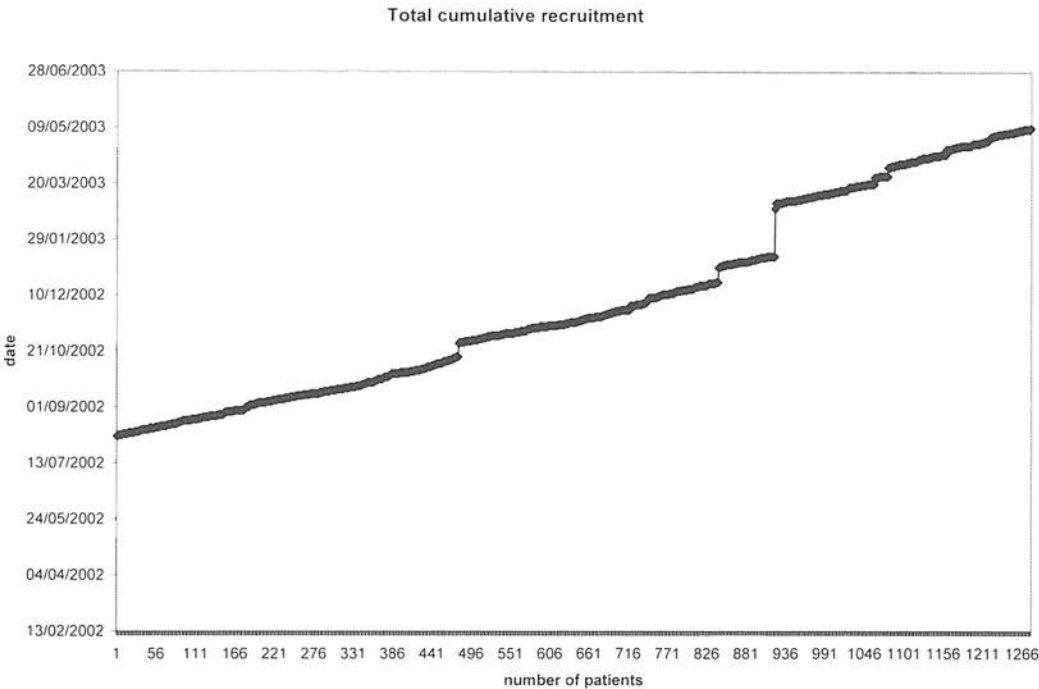
**(viii) *Minimal myocyte necrosis***

Patients that were TnI positive but DE negative (24).

# 5 Results

## 5.1 Screening data

One thousand two hundred and seventy eight patients were screened between 6<sup>th</sup> August 2001 and 9<sup>th</sup> May 2002 **Figure 5-1**. Eight hundred and ninety one (70%) were admitted to the medical receiving ward and 387 (30%) were admitted to the coronary care unit.



**Figure 5-1: Cumulative screening data for all patients**

Three distinct gaps in the consecutive nature of screening can be seen. The first was due to MRI scanner disrepair, the second due to annual leave and the third due to an annual MRI scanner service. These match the gaps on the graph of cumulative recruitment rate shown in **Figure 5-2**. The mean (SD) age of the screened population was 68 (15) years and 704 (55%) were male. Eleven hundred and twenty five patients (88%) were excluded from the study with

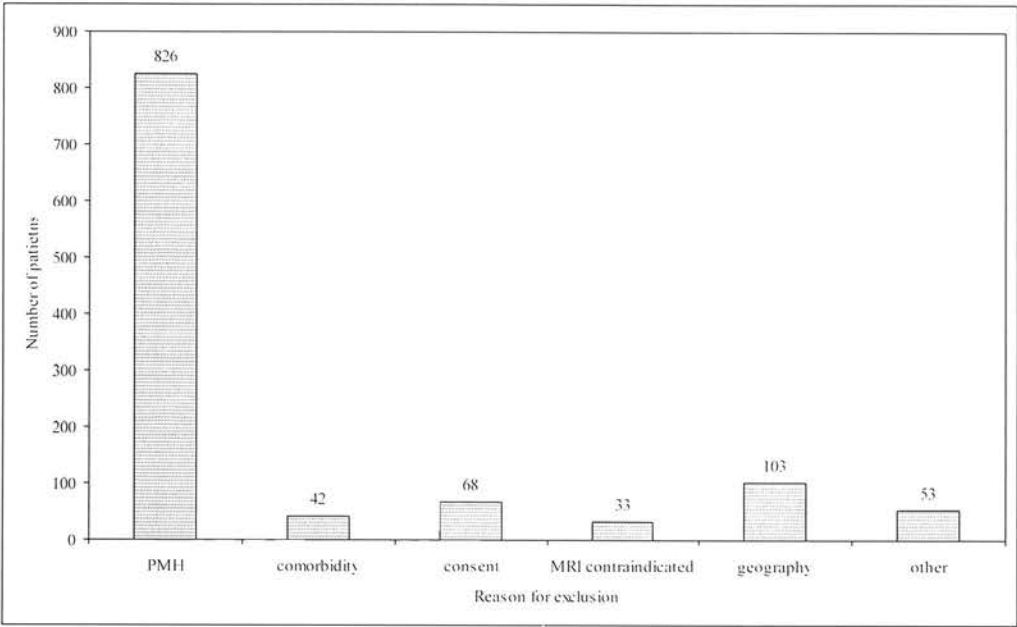
a mean (SD) age of 70 (15) years and 602/1125 (54%) were male. For a total of 281 (22%) patients this was their first significant episode of chest pain.



**Figure 5-2: Cumulative recruitment data for study population**

The reasons for exclusion of the 1125 patients are shown in **Figure 5-3**. Eight hundred and twenty six (73%) were excluded due to a past medical history of chest pain. Of these forty nine (6%) had had Coronary Artery Bypass Graft surgery (CABG), 410 (50%) had a history of angina (5 patients already in the study from previous admission), 106 (13%) had a definite diagnosis of previous myocardial infarction, 261 (31%) had a history of hospital admission for non specific chest pain.

Forty two patients (4%) were excluded due to significant comorbidity. Nine died, 12 were too unwell and 21 had a diagnosis of active cancer.



**Figure 5-3: Total exclusions from study by reason**

Sixty eight patients (6 %) were excluded for reasons of consent. Fifteen were unable due to dementia, learning difficulties or language issues. One was in police custody and 52 refused to take part in the study (9 took their own discharge).

Thirty three (3 %) had one of the listed contraindications to ceMRI. Four had a pacemaker in place, 10 had a previous procedure and implant that was non-compatible. Sixteen stated that they were claustrophobic and two felt they would be unable to lie still due to back pain, one was too heavy.

One hundred and three patients (9 %) were excluded due to reasons of geography, meaning that they were transferred from another hospital or on holiday and so presented too late or would not be able to return for follow up. The remaining 53 (5 %) are classified as other due to missing data.

## 5.2 Final study population

One hundred and fifty three patients with a mean (SD) age 56 (13) years met the study criteria and were recruited between August 2002 and May 2003, 102/153 (67%) were male and 57 (37%) had a single acute MI by a combination of ceMRI and biomarkers, **Table 5-1**.

Cardiovascular risk profile was in keeping with previous studies on ACS: smokers = 103/153 (67%); positive family history = 70/153 (46%); diabetes mellitus = 19/153 (12%); hypertension = 53/153 (35%); and hypercholesterolaemia = 33/153 (22%). The mean (SD) TIMI risk score was 2.6 (1.2) with all patients scoring one point for chest pain. By presenting ECG; 37/153 (24%) had ST elevation and 26/153 (17%) had ST depression. Seventy eight (52%) went on to have inpatient diagnostic coronary angiography and 58 (38 %) had  $\geq 1$  region of significant stenosis. The total population had a mean BMI of 27 which would be classified as “overweight”. The mean serum cholesterol was greater than 5 mmol/l and over half were discharged on primary or secondary cardiovascular prevention drugs with nearly  $\frac{3}{4}$  on aspirin.

When demographic and selected clinical characteristics of patients with single AMI are compared to those with “non” single AMI, patients in the single AMI group had a higher proportion of ST elevation (47 vs. 10 %,  $p<0.001$ ) and ST depression (30 vs. 9 %,  $p<0.001$ ) on the presenting ECG **Table 5-1**. Therefore 23% of patients in the single AMI group had no evidence of ST deviation on the presenting ECG.

Table 5-1: Demographic and clinical characteristics for whole population and by presence of single AMI

	Total population (n=153)	Single AMI (n=57)	Non single AMI (n=96)	p value
<i>Continuous variables</i>				
Age, years	56.3 (12.8)	59.8 (12.5)	54.2 (12.5)	0.08
Systolic BP	125.6 (19.7)	123.3 (18.6)	127.1 (20.3)	0.243
Diastolic BP	77.3 (12.8)	75.9 (12.8)	78.1 (12.8)	0.297
BMI	26.9 (4.7)	26.9 (4.0)	27.0 (5.1)	0.865
TIMI risk score	2.6 (1.2)	3.5 (0.9)	2.1 (1.1)	<0.001
Time from pain to MRI, hrs	54.7 (32.0)	63.6 (22.8)	49.3 (35.4)	0.003
Median (IQR) CK, IU/ml	172 (85 - 695)	736 (332-2136)	111 (77-188)	<0.001
Median (IQR) TnI, ng/ml	0.7 (0-27.9)	29.8 (11.4-64.9)	0 (0-0)	<0.001
Cholesterol, mmol/l	5.6 (1.25)	5.6 (1.24)	5.6 (1.27)	0.963
Median (IQR) glucose,	6.2 (5.3-7.7)	7.0 (6.1-8.9)	5.7 (5.2-7.4)	<0.001
Median (IQR) urea,	5.4 (4.5-6.5)	5.6 (4.7-7.1)	5.2 (4.5-6.3)	0.067
Median (IQR) creatinine,	103 (84.5-108)	104 (92.5-111)	94.5 (82-104)	<0.001
<i>Categorical variables</i>				
Sex, m	102 (66.6)	43 (75.4)	59 (61.5)	0.076
Smoker	103 (67.3)	40 (70.2)	63 (65.6)	0.562
Family history	70 (45.7)	22 (38.6)	48 (50)	0.171
Diabetes	19 (12.4)	5 (8.8)	14 (14.6)	0.292
Hypertension	53 (34.6)	21 (36.8)	32 (33.3)	0.659
Hypercholesterolaemia	33 (21.6)	11 (19.3)	22 (22.3)	0.599
Admission ECG:				
ST elevation	37 (24.2)	27 (47.4)	10 (10.4)	<0.001
ST depression	26 (17.0)	17 (29.8)	9 (9.4)	<0.001
Q waves	6 (3.9)	0 (0)	6 (6.3)	0.054
Discharge Drugs:				
Aspirin	112 (73.4)	57 (100)	58 (60.2)	<0.001
Beta blocker	90 (58.9)	49 (86.4)	43 (45.0)	<0.001
ACE inhibitor	49 (32.3)	35 (61.4)	16 (16.7)	<0.001
Statin	85 (55.6)	55 (97.7)	32 (33.3)	<0.001
Admission cor. angio:				
Performed	78 (51.8)	41 (71.9)	37 (38.5)	<0.001
Sig. stenosis	58 (38.0)	37 (64.9)	21 (21.9)	<0.001

All available data used. Data presented as mean (SD) for continuous variables and number (%) for categorical variables, unless otherwise stated. Comparisons made between the 2 groups single AMI and non single AMI. Two sample t-test used for continuous variables and chi-squared test, categorical. The Mann-Whitney test was used for non-normal data. Significant coronary artery stenosis defined as >70% in major coronary vessel. BP, blood pressure; BMI, body mass index, TIMI, thrombolysis in myocardial infarction; CKMB, creatine kinase MB; TnI, troponin I, MRI, magnetic resonance imaging; ECG, electrocardiogram, ACE, angiotensin converting enzyme

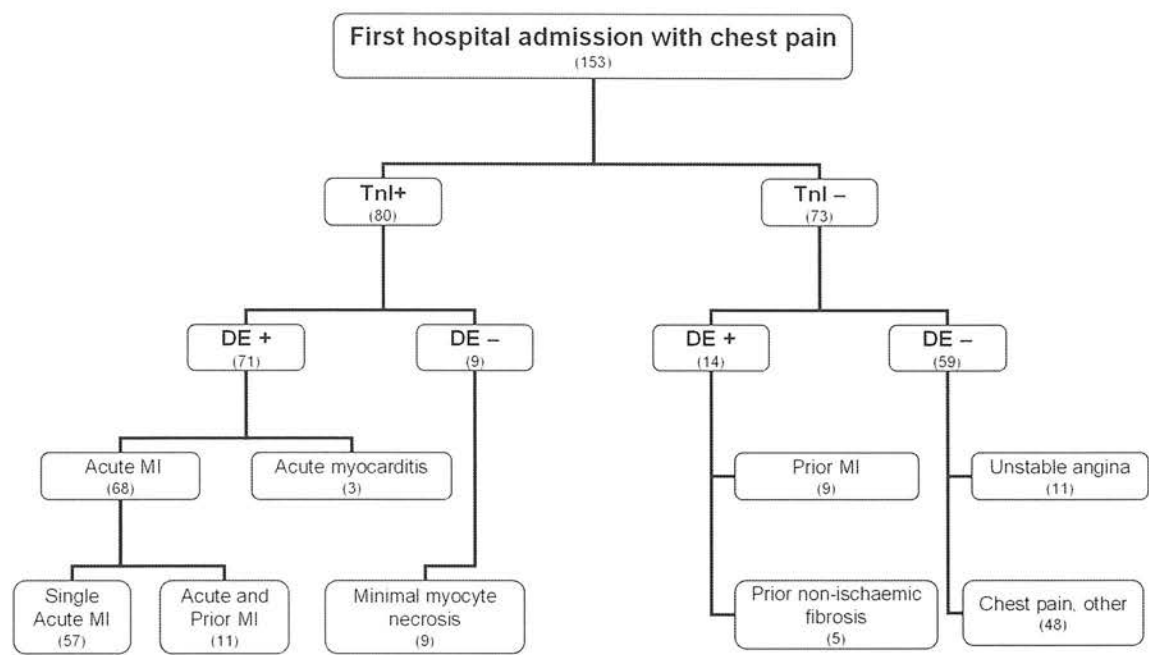
Patients in the single AMI group had higher TnI (median 30 vs. 0.0 g,  $p<0.001$ ) and CK (median 736 vs. 111 IU/ml,  $p<0.001$ ) levels and higher TIMI risk scores (mean 3.5 vs. 2.1,  $p<0.001$ ). A coronary angiogram was more likely to be performed as an inpatient (72 vs. 39 %,  $p<0.001$ ) and there was a greater proportion with a significant stenosis (37/41 (90%) vs. 21/37 (57%),  $p<0.001$ ). There was a longer interval from onset of chest pain until the initial ceMRI study was performed (64 vs. 49 h,  $p=0.003$ ). Patients with single AMI had a higher admission glucose (7.0 vs. 5.7 mmol/L,  $p<0.001$ ). A random blood glucose of 7.0 mmol/L (126 mg/L equivalent) is above normal but not within the range of “pre-diabetes” (140-200 mg/L) (167). Patients with a single AMI had a higher serum creatinine (104 vs. 95  $\mu$ mol/L,  $p<0.001$ ) the significance of which is uncertain as both are within normal limits. In the single AMI group aspirin, beta blocker and statin use were high (>85% for each) but ACE inhibitor prescription less (61%) and in all cases greater than the non-single AMI group.

#### **Final study population divided by discharge diagnosis based on a combination of TnI and ceMRI.**

Of the 153 patients that met study inclusion criteria, 80 (52%) were TnI positive (*TnI+*), **Figure 5-4**. Within this group, 71 (89%) were also DE positive (*DE+*). Of the 71 *DE+* patients, 68 (96%) had a subendocardial DE pattern (*acute MI*) and 3 (4%) had the subendocardial sparing pattern (*acute myocarditis*). Of the 68 acute MI patients, 57 (84%) had a single discrete region of DE (*single Acute MI*) and 11(16%) had > 1 region. The assumption is that at least one of the regions in the latter group is due to a prior event (*acute and prior MI*). Of



the 80 TnI+ patients coronary angiography was performed in 59 (73%) and significant stenosis was seen in 49 (61%). Nine (11%) patients were TnI+ but DE negative (DE-) and were classified as minimal myocyte necrosis (168).



**Figure 5-4: Study patients divided by discharge diagnosis based on TnI and ceMRI**

Of the 153 patients that met study inclusion criteria, 73 (48%) were TnI negative (*TnI*-), **Figure 5-4**. Fourteen of these (19%) were positive for DE (*DE*+); 9 patients (64%) had subendocardial DE (*prior MI*) and 5 (36%) had subendocardial sparing of DE (*prior non-ischaemic fibrosis*). Fifty nine (81%) of the TnI negative patients were DE negative (*DE*-). In this group, 11 (19%) had a diagnosis of *unstable angina* and 48 (81%) had a diagnosis of “*chest pain, other*”. Coronary angiography was performed in 20 (27%) and significant stenosis was seen in 8

(11%), all eight were part of the unstable angina group. In total eighty five (56%) of patients had hyperenhancement on ceMRI (DE+).

Left ventricular structure and function in the final study population

Six month follow up scans were performed in 103 patients (67%) from the total population; 38 (67%) of the single AMI group and 65 (68%) of the non-single AMI group, Table 5-2.

Table 5-2: Baseline and follow up left ventricular structure and function by ceMRI

	Total Scan 1, n=153; Scan 3, n=103	Single AMI Scan 1, n=57 Scan 3, n=38	Non single AMI Scan 1, n=96 Scan 3, n=65	p value
<i>LV structure and function</i>				
LVEF, %. Visit 1	60.8 (11.6)	55.9 (10.9)	63.7 (11.1)	<0.001
LVEF, %. Visit 3	61.5 (12.4)	54.8 (13.0)	65.4 (10.3)	<0.001
LVESV, ml. Visit 1	56.9 (38.0)	63.2 (25.3)	53.2 (43.4)	0.076
LVESV, ml. Visit 3	64.6 (48.9)	86.0 (54.8)	51.9 (39.9)	<0.001
LVEDV, ml. Visit 1	138.6 (45.5)	140.9 (37.6)	137.2 (49.7)	0.607
LVEDV, ml. Visit 3	156.1 (56.2)	181.1 (59.1)	141.1 (49.3)	<0.001
Remodeller by LVEDV	29 (18.9)	15 (26.3)	14 (14.6)	0.073
LV mass, g. Visit 1	127.7 (43.0)	130.4 (38.3)	126.1 (45.7)	0.535
LV mass, g. Visit 3	138.5 (43.3)	138.3 (42.1)	134.8 (46.7)	0.174

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Comparisons made between the 2 groups single AMI and non single AMI. Two sample t-test used to compare continuous variables and chi-squared test for categorical. Remodeller defined as an increase from baseline of >20%. LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume.

LVEF was significantly lower in the single AMI group both at baseline (56 vs. 64 %,  $p<0.001$ ) and at 6 months (55 vs. 65 %,  $p<0.001$ ). At baseline the individual LV dimensions measured were similar although there was a trend towards a larger LVESV in the single AMI group (mean 63 vs. 53 ml,  $p=0.076$ ).

At follow up 6 months later both LVESV (mean 86 vs. 52 ml,  $p<0.001$ ) and LVEDV (mean 181 vs. 141 ml,  $p<0.001$ ) were significantly greater in the single AMI group and there was a trend towards LV remodelling ( $>10\%$  increase) (26 vs. 15 %,  $p=0.07$ ). The inhomogeneity of the non-single AMI group will have contributed to this lack of difference in remodelling; the 14 patients that remodel from this group included those with dilated cardiomyopathy and prior MI on admission. There was no difference in LV mass either at baseline or at follow up.

### 5.3 ST-segment deviation analysis of the admission 12-Lead ECG as an aid to early diagnosis of AMI with a ceMRI gold standard

This section describes the results from the sub study population consisting of 116 patients after 35 were excluded because of confounding factors on the admission ECG.

**Table 5-3** presents the baseline demographic and clinical characteristics of this study population divided into AMI ( $n = 58$ ) and non-AMI ( $n = 58$ ) groups. Eight patients with multiple infarcts are included in this study. Patients in the AMI group were older (mean 59 vs. 53 years,  $p = 0.0077$ ) and there was a shorter duration of time from the onset of chest pain to the ECG (median 2.7 vs. 7.4 h,  $p = 0.02$ ). There was a longer interval until the initial ceMRI study (median 64 vs. 33 hours,  $p = 0.0001$ ) in the AMI group. Slightly more than one half (54%) of the AMI group and few (5%) of the non-AMI group received reperfusion therapy. Any reference to reperfusion therapy is based on the GUSTO ECG criteria as dictated by the local protocol. All STEMI patients received thrombolysis, except 2 who underwent primary percutaneous intervention.

Table 5-3: Demographic and clinical characteristics according to ceMRI diagnosis of AMI

	AMI Positive by ceMRI (n=58)	AMI Negative by ceMRI (n=58)	p value
<i>Continuous variables</i>			
Median (IQR) AMI size, g	27.1 (13.9-45.4)	-	-
Median (IQR) AMI size, % LV mass	23.8 (12.4-38.8)	-	-
Age, yrs*	59.1 (13.2)	52.8 (11.7)	0.0077
Median (IQR) time to ECG, hourst	2.7 (1.8-9.6)	7.4 (2.3-20.5)	0.020
Median (IQR) time to MRI scan, hourst	63.6 (45.3-85.0)	32.6 (26.0-58.2)	<0.0001
Weight, kg*	79.6 (17.1)	81.8 (15.9)	0.46
BP systolic, mmHg*	121.6 (17.9)	127.3 (19.7)	0.11
BP diastolic, mmHg*	73.4 (10.7)	79.6 (14.2)	0.0084
Heart rate, beats/ min*	53.7 (11.1)	58.0 (11.8)	0.049
LVEF, %*	57.0 (10.5)	64.4 (9.0)	<0.0001
Median (IQR) Tnl, ng/mL†	43.1 (12.7-64.9)	0 (0-0)	<0.0001
Median (IQR) peak CK, IU/mL†	733 (383-1942)	102 (74-162)	<0.0001
Median (IQR) peak CKMB, IU/mL†	56.0 (14.0-111.0)	1.0 (0.5-1.6)	<0.0001
Median (IQR) CRP, mg/l†	36.0 (14.0-91.0)	6.0 (0-11.0)	<0.0001
<i>Categorical variables</i>			
Male*	39 (67.2)	36 (62.1)	0.56
Smoking*	40 (72.7)	39 (68.4)	0.62
Reperfusion Therapy*	31 (54.4)	3 (5.2)	<0.0001
Infarct location:			
Anterior	13 (22.4)	-	-
Inferior	20 (34.5)	-	-
Lateral	11 (19.0)	-	-
Inferior and Lateral	6 (10.3)		
Multiple	8 (13.8)	-	-

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated.

\*Two-sample t-test used to compare continuous variables and chi-squared test for categorical. †Wilcoxon rank sum test used for non-normal data.

There were 10 patients that were falsely positive by ECG and/or troponin I for AMI considering ceMRI as the gold standard **Table 5-4**. In the 8 patients falsely positive by troponin I, the peak value was 4.4 ng/ml and the mean (SD) was 1.44 (1.38) ng/ml. In the 2 falsely positive patients by ECG alone, 1 had a clinical diagnosis of pericarditis and the other had neither clinical nor angiographic evidence of cardiac disease. Eight of these 10 patients could be considered to have had minimal myocyte necrosis or “necrosette” (i.e., an extremely small MI with a low peak troponin I) (169).

**Table 5-4: False positives by Troponin I and/ or ECG criteria**

Patient Group	TnI (ng/ml)	ECG	Coronary angiography	Clinical diagnosis
<i>By TnI</i>				
	1.9	Negative	Normal	Minimal myocyte necrosis
	1.3	Negative	NA	Minimal myocyte necrosis
	0.3	Negative	Normal	Minimal myocyte necrosis
	0.3	Negative	95% stenosis LCx	Minimal myocyte necrosis
	0.4	Negative	95% stenosis RCA	Minimal myocyte necrosis
	0.9	Negative	NA	Minimal myocyte necrosis
<i>By ECG</i>				
	< 0.2	ACC/ ESC STEMI	NA	Pericarditis
	<0.2	STEMI equivalent	Normal	Non-cardiac chest pain
<i>By both TnI and ECG</i>				
	4.4	ACC/ ESC STEMI	Normal	Takotsubo
	2	STEMI equivalent	95% stenosis RCA	Minimal myocyte necrosis

ECG criteria as described in text, table indicates by which criteria patient was falsely positive  
ACC/ ESC, American College of Cardiology/ European Society of Cardiology, NA, not applicable (coronary angiography not performed); STEMI, ST elevation myocardial infarction

The performances of the GUSTO and ACC/ESC STEMI criteria are almost identical, with only a single patient in both the AMI and non-AMI groups being classified differently. Therefore, for the remainder of the data analysis, only the more recently published STEMI criteria (ACC/ESC) are considered. Only 50% (29 of 58) of the AMI group are identified by the ACC/ESC STEMI criteria, but an additional 34% (49 of 58) are identified by the STEMI-equivalent ST-segment depression criteria increased the sensitivity from 50% to 84% ( $p = 0.0001$ ) and reduced the specificity from 97% and 93% ( $p = 0.50$ ). Positive and negative predictive values are also shown and have been calculated with an infarct prevalence of 50% in this population **Table 5-5**.

**Table 5-5: Comparison of ECG criteria with ceMRI scan**

AMI detected by ECG guidelines		MI detected by ceMRI		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value
		Yes (n=58)	No (n=58)				
GUSTO STEMI criteria	Yes	28	1	0.48 (0.35,0.62)	0.98 (0.91,1.00)	0.96	0.65
	No	30	57				
ACC/ESC STEMI criteria	Yes	29	2	0.50 (0.37,0.63)	0.97 (0.88,1.00)	0.94	0.66
	No	29	56				
ACC/ESC STEMI and STEMI equivalent criteria	Yes	49	4	0.84 (0.73,0.93)	0.93 (0.83,0.98)	0.92	0.85
	No	9	54				

CI = confidence interval, other abbreviations as in Table 5.21 and 5.2

**Table 5-6** presents the characteristics of the ceMRI-positive patients stratified according to detection by the ACC/ESC STEMI criteria (n = 29) and by the STEMI-equivalent ST-segment depression criteria only (n = 20). There is markedly longer delay from time of symptom onset until the initial ECG in the STEMI-equivalent group (median 5.5 h) than in the STEMI group (median 2.2 h [p = 0.0075]).

The AMI sizes estimated by the various biochemical markers are similar between the 2 ECG detection groups. There was a tendency toward lower LVEF in those detected by the STEMI criteria (54%) than in those detected by the STEMI-equivalent criteria only (59%) (p = 0.14), but it should be noted that both these values are within normal limits. However, as indicated, most (86%) in the STEMI group but few (26%) in the STEMI-equivalent group received reperfusion therapy. There was no significant difference in the presence or absence of MVO or transmuralty or presence of multiple infarcts between the 2 groups. There was also no significant difference in the distribution of infarct locations between the 2 groups.



Table 5-6: Comparison of demographic and clinical characteristics of ceMRI verified myocardial infarctions present by ST deviation ACC/ESC criteria

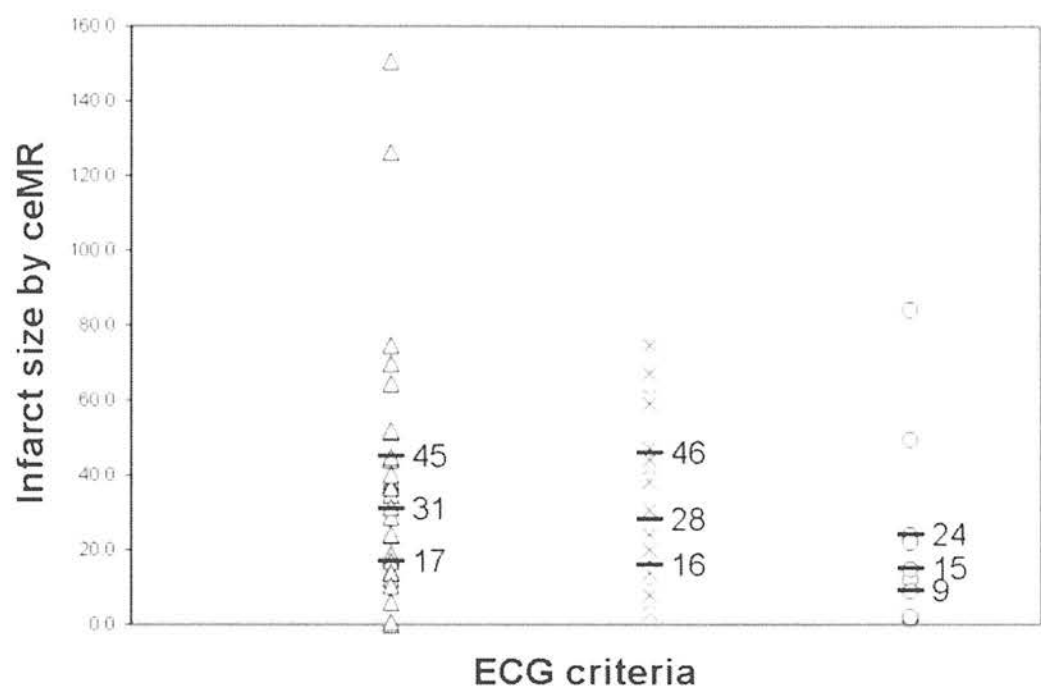
	CeMRI verified AMI detected by ACC/ESC STEMI criteria (n= 29)	CeMRI verified AMI detected by STEMI equivalent criteria only (n=20)	p value
<i>Continuous variables</i>			
Median (IQR) Infarct size, g*	31.2 (17.0-44.6)	27.9 (16.4-46.3)	0.96
Median (IQR) Infarct size, % LV mass*	23.8 (13.9-36.3)	26.1 (14.5-38.8)	0.93
Age, years*	55.7 (12.7)	58.9 (13.0)	0.41
Median (IQR) time to admission ECG, h†	2.2 (1.3-3.8)	5.5 (2.2-17.1)	0.0075
Median (IQR) time to ceMRI scan, h*	67.1 (50.1-89.1)	73.2 (50.1-86.5)	1.00
Weight, kg	80.3 (16.5)	79.7 (17.9)	0.91
Systolic BP, mm Hg	120.0 (16.9)	122.4 (19.6)	0.65
Diastolic BP, mm Hg	72.6 (10.4)	75.1 (11.3)	0.43
Heart rate, beats/ min	54.2 (13.4)	53.4 (9.6)	0.81
LVEF, %	54.0 (10.3)	58.6 (9.9)	0.14
Median (IQR) peak Tnl, ng/mL†	43.8 (25.8-68.5)	43.7 (12.4-56.0)	0.34
Median (IQR) peak CK, IU/mL†	746 (496-2057)	989 (342-1850)	0.78
Median (IQR) peak CKMB, IU/mL†	55.1 (15.6-172.1)	61.2 (12.3-118.5)	0.88
Median (IQR) CRP, mg/l†	48.5 (16.0-107.0)	35.0 (11.0-85.0)	0.61
<i>Categorical variables</i>			
Male	21 (72.4)	14 (70.0)	0.85
Smoking†	20 (74.1)	14 (73.7)	1.00
Reperfusion Therapy	25 (86.2)	5 (26.3)	<0.0001
MVO	10 (37.0)	6 (31.6)	0.70
Transmurality†	21 (75.0)	12 (70.6)	0.74
Infarct location†			
Anterior	5 (18.5)	4 (20.0)	0.22*
Inferior	14 (51.8)	5 (25.0)	-
Posterior	4 (14.8)	5 (25.0)	-
Inferior and Posterior	1 (3.7)	3 (15.0)	-
Multiple	3 (11.1)	3 (15.0)	-

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated.

\*Two-sample t-test used to compare continuous variables and chi-squared test (or Fisher Exact test as appropriate) for categorical. †Wilcoxon rank sum test used for non-normal data.

BP, blood pressure; ECG, electrocardiogram; CK, creatine kinase; CKMB, creatine kinase MB isoenzyme; CRP, C reactive protein; LVEF, left ventricular ejection fraction; MRI=magnetic resonance imaging; Tnl, troponin I. \*Multiple category not included in test.

The comparative ceMRI-determined AMI sizes in the 2 ECG diagnostic groups are similar (median 31 vs. 28 g or 24% vs. 26% of the LV mass), **Figure 5-5**. This result is in contrast to the trend ( $p = 0.29$ , Kruskal-Wallis test) to smaller AMI sizes in the group of 9 patients in whom even the STEMI equivalent criteria were not present.



Comparative acute myocardial infarction (AMI) sizes (g) with median and interquartile ranges for 3 groups divided according to American College of Cardiology/ European Society of Cardiology (ACC/ ESC) criteria: detected by ST-segment elevation myocardial infarction (STEMI) criteria only (**open triangles**); detected by STEMI-equivalent criteria only (**x**), and AMI missed by both criteria (**open circles**). ECG = electrocardiographic.

**Figure 5-5: Comparative AMI sizes with ECG Criteria**

## 5.4 Validation of ECG and biochemical estimates of first AMI size using a ceMRI gold standard

Thirty three (58%) of the 57 patients with a single AMI received emergency reperfusion therapy **Table 5-7**, a group that is synonymous with “STEMI”. Patients in the reperfused group were younger (mean 57 vs. 64 years,  $p=0.047$ ), had higher systolic (130 vs. 118,  $p=0.02$ ) and diastolic (80 vs. 73,  $p=0.04$ ) blood pressures than the non-reperfused group (that is synonymous with “NSTEMI”). AMI sizes by both biomarkers (CK-MB, TnI) and ECG (Selvester score) were larger in the reperfused group. The incidence of ST elevation (STE) was higher (73 vs. 13 %,  $p<0.001$ ) and ST depression lower (18 vs. 46 %,  $p=0.02$ ).

Aspirin, beta blocker and statin prescribing rates were similar for both groups and all over 80%. More patients in the reperfused group were discharged on an ACE inhibitor (77% vs. 39%,  $p=0.01$ ). Males made up over 75% of the population and patients in both groups had a similar risk factor profile with over 65% being current smokers.

Table 5-7: Demographic and clinical characteristics for single AMI population and according to immediate reperfusion therapy

	Total (n=57)	Reperfused (n=33)	Non reperfused (n=24)	p value
<i>Continuous variables</i>				
Age, years	59.8 (12.5)	57.0 (13.0)	63.7 (11.0)	0.047
Systolic BP	123.3 (18.6)	118.4 (16.4)	130.0 (19.7)	0.02
Diastolic BP	75.9 (12.8)	72.9 (11.9)	79.9 (13.2)	0.04
BMI	26.9 (4.0)	26.9 (4.3)	26.8 (3.6)	0.91
TIMI risk score	3.5 (0.9)	3.5 (0.7)	3.5 (1.1)	0.85
Time from pain to MRI	63.6 (22.8)	62.6 (21.4)	65.0 (25.1)	0.70
Median (IQR) CKMB, IU/ml	68 (19 – 131)	96 (42 – 226)	40 (15 – 100)	0.04
Median (IQR) TnI, ng/ml	29.8 (11.4–64.9)	46.4 (23.5 – 116.7)	14.5 (10.2 – 32.4)	0.001
Median (IQR) Selvester score	3 (1-6)	4 (2 – 7.25)	3 (0-5)	0.04
<i>Categorical variables</i>				
Sex, male	43 (75.4)	25 (75.7)	18 (75)	0.71
Smoker	40 (70.2)	24 (72.7)	16 (66.6)	0.62
Family history	22 (38.6)	12 (36.3)	10 (41.7)	0.68
Diabetes	10 (17.5)	7 (21.2)	3 (12.5)	0.53
Hypertension	21 (36.8)	11 (33.3)	10 (41.7)	0.52
Hypercholesterolaemia	11 (19.3)	5 (15.1)	6 (25.0)	0.35
Admission ECG:				
ST elevation	27 (47.4)	24 (72.7)	3 (12.5)	<0.001
ST depression	17 (29.8)	6 (18.2)	11 (45.8)	0.02
Discharge Drugs:				
Aspirin	57 (100)	33 (100)	24 (100)	-
Beta blocker	49 (86.4)	28 (84.6)	19 (88.9)	0.69
ACE inhibitor	35 (61.4)	25 (76.9)	10 (38.9)	0.01
Statin	55 (97.7)	32 (96.1)	24 (100)	0.4

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Comparisons made between the 2 groups reperfusion and non reperfusion. Two sample t-test used to compare continuous variables and chi-squared test for categorical. Wilcoxon rank sum test used for non-normal data.  
BP, blood pressure; BMI, body mass index, TIMI, thrombolysis in myocardial infarction; CKMB, creatine kinase MB isoenzyme; TnI, troponin I, MRI, magnetic resonance imaging; ECG, electrocardiogram, ACE, angiotensin converting enzyme

By ceMRI, patients with a single AMI that had received emergency reperfusion therapy had significantly larger infarct sizes both on admission (mean 44g vs. 21g,  $p=0.001$ ) and at mean of 38 days follow up (mean 31g vs. 13g,  $p=0.004$ ) **Table 5-8**. This size difference was consistent in all dimensions of acute infarct size. A higher than expected proportion of patients had a transmural infarct; over three quarters (77%) of the total population had a least one segment with an infarct transmurality that was over 50% of the wall thickness (mean = 3.5/4).

**Table 5-8: Baseline and follow up infarct characteristics and left ventricular structure and function by cardiac ceMRI**

	Total (Scan 1, n=57 2, n=43 3, n=38)	Reperused (Scan 1, n=33 2, n=26 3, n=25)	Non reperused (Scan 1, n=24 2, n= 17 3, n=13)	p value
<i>Infarct characteristics</i>				
Infarct size, g. Visit 1	34.7 (28)	44.4 (31)	21.3 (18)	0.001
Infarct size, g. Visit 2	24.2 (21)	31.3 (23)	13.4 (13)	0.004
Endocardial extent	90.7 (43.9)	98.5 (43.3)	79.5 (43.2)	0.11
Transmurality score	3.5 (0.8)	3.7 (0.7)	3.1 (0.9)	0.02
Transmurality $\geq 3$	44 (77.2)	29 (88.1)	15 (62.2)	0.02
Number of slices	6.3 (2.4)	7.1 (2.0)	5.2 (2.5)	0.002
Number of segments	5.4 (2.7)	6.4 (2.5)	4.1 (2.5)	0.001
Early MVO	35 (61.4)	24 (72.7)	11 (45.8)	0.04
Late MVO	22 (38.6)	17 (51.5)	5 (20.8)	0.02
<i>LV structure and function</i>				
LVEF, %. Visit 1	55.9 (10.9)	53.8 (11.9)	58.7 (8.9)	0.09
LVEF, %. Visit 3	54.8 (13.0)	51.4 (12.2)	61.3 (12.4)	0.02
LVESV, ml. Visit 1	63.2 (25.3)	67.6 (26.4)	57.0 (23.4)	0.125
LVESV, ml. Visit 3	86.0 (54.8)	95.7 (61.9)	67.8 (35.5)	0.08
LVEDV, ml. Visit 1	140.9 (37.6)	144.6 (36.4)	135.7 (39.4)	0.38
LVEDV, ml. Visit 3	181.1 (59.1)	186.3 (66.1)	171.0 (43.2)	0.45
LV mass, g. Visit 1	130.4 (38.3)	132.1 (37.8)	127.9 (39.5)	0.68
LV mass, g. Visit 3	138.3 (42.1)	137.5 (41.5)	140.0 (44.9)	0.86

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Comparisons made between the 2 groups reperfusion and non reperfusion. Two sample t-test used to compare continuous variables and chi-squared test for categorical. Wilcoxon rank sum test used for non-normal data.  
MVO, microvascular obstruction; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; LVEDV, left ventricular end diastolic volume.

The total incidence of MVO was higher in the reperfused group, a result that would be in keeping with the larger infarct sizes. In both groups early MVO was detected more frequently than late MVO (reperfused, 73 vs. 52% and non-reperfused, 46 vs. 21 %). The proportion of MVO defined as late MVO was higher in the reperfused group than in the non-reperfused group (17/24 (71%) vs. 5/11 (45%),  $p < 0.001$ ).

There were significant reductions in infarct size between admission and mean 38 days: by 30 % in the total population ( $p < 0.001$ ); by 30% ( $p < 0.001$ ) in the reperfused group; and by 37% ( $p = 0.001$ ) in the non-reperfused group.

There was no difference in LVEF between the groups on admission although there was a trend to a lower LVEF in the reperfused group (54 vs. 59 %,  $p = 0.09$ ). By mean 203 days the difference in LVEF was significant (51 vs. 61 %,  $p = 0.02$ ). LVEF remained stable between admission and mean 203 days when considering the whole group.

Both the Selvester score and biomarkers correlate moderately well with acute infarct size by ceMRI in all cases and the correlation coefficient is better in the reperfused group Table 5-9, **Figure 5-6**. In the non-reperfused group TnI ( $r = 0.43$ ,  $p = 0.05$ ) and CKMB ( $r = 0.54$ ,  $p = 0.02$ ) correlated with infarct size. The Selvester score has a significant albeit weak correlation with TnI in reperfused infarcts only ( $r = 0.5$ ,  $p = 0.01$ ).

When correlations are made with final infarct size (at 38 days) there is an improvement in most  $r$  values: Selvester score (all:  $r = 0.59$  up to  $0.69$ ,  $p = 0.47$ ; reperfused:  $r = 0.61$  up to  $0.72$ ,  $p = 0.5$ ; non-reperfused:  $0.31$  up to  $0.67$ ,  $p = \text{NA}$  (sample size too small)); TnI (all:  $r = 0.69$  up to  $0.75$ ,  $p = 0.93$ ; non-reperfused:  $r = 0.43$  up to  $0.78$ ,  $p = 0.09$ ). The contrary was found regarding the

correlation between TnI and infarct size in the reperfused group where the r value fell from 0.7 to 0.59, p=0.5 between admission and mean 38 days.

Table 5-9: Correlation between selected measures of acute and final infarct size by acute reperfusion status

Comparisons	All cases		Reperfusion		No reperfusion	
	r	p	r	p	r	p
<i>Acute Infarct size</i>						
Infarct size, g v Selvester	0.59 (n=47)	<0.001	0.61 (n=30)	<0.001	0.31 (n=17)	0.23
Infarct size, g v TnI (ng/ml)	0.69 (n=47)	<0.001	0.7 (n=26)	<0.001	0.43 (n=21)	0.05
Infarct size, g v CKMB (IU/ml)	0.60 (n=45)	<0.001	0.62 (n=27)	0.001	0.54 (n=18)	0.02
Selvester v TnI (ng/ml)	0.514 (n=39)	0.001	0.5 (n=25)	0.01	0.33 (n=14)	0.25
<i>Final Infarct size</i>						
Infarct size, g v Selvester	0.69 (n=33)	<0.001	0.72 (n=23)	<0.001	0.67 (n=10)	0.03
Infarct size, g v TnI (ng/ml)	0.75 (n=36)	<0.001	0.59 (n=22)	0.004	0.78 (n=14)	0.001

All available data used. Data are presented by number (n) suitable for analysis, Spearman’s rank correlation coefficient (r) and significance (p).

TnI, troponin I; CKMB, creatine kinase muscle brain isoenzyme; LVEF, left ventricular ejection fraction

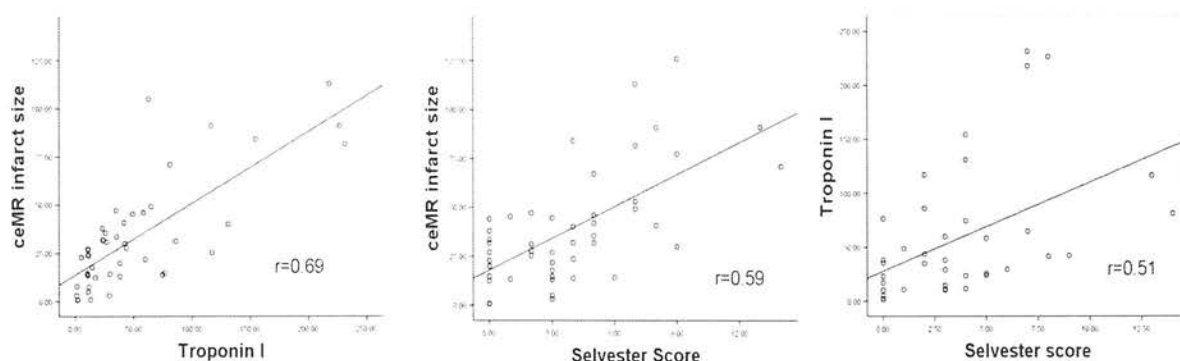


Figure 5-6: Individual correlations between ceMRI infarct size and Selvester score and TnI for the total population

To investigate if the combination of TnI and Selvester score improved the correlation with ceMRI derived infarct size a multiple linear regression model was formed. This included TnI first then the Selvester score was added Table 5-10.

Table 5-10: The association between TnI alone and in combination with Selvester score with ceMRI derived admission and final infarct sizes

		All		Reperfused		Non reperfused	
		R	F change	R	F change	R	F change
Admission infarct size	TnI	0.71	<0.001	0.72	<0.001	0.28	0.33
	TnI plus Selvester	0.80	<0.001	0.82	0.003	0.43	0.25
Final infarct size	TnI	0.60	0.01	0.55	0.009	0.58	0.17
	TnI plus Selvester	0.80	<0.001	0.77	0.002	0.82	0.11

All available data used. Data are presented as R, Pearson correlation and the significance of F change model 1 from control and model 2 with addition of Selvester to TnI.



For the admission infarct size the Pearson correlation is seen to improve for the total population from 0.71 to 0.8, F change  $<0.001$ . There is improvement in both subgroups but only in the reperfused group is the addition of Selvester score to TnI significant 0.72 to 0.82, F change =0.003).

A similar pattern is seen when TnI and Selvester are used to predict final infarct size at mean 38 days. For the total population the correlation rises from 0.6 to 0.8, F change  $<0.001$ . There was improvement in both subgroups but only in the reperfused group is the addition of Selvester score to TnI significant 0.55 to 0.77, F change =0.002.

The numbers are small when looking at the subgroups so no further comment can be made other than that the trend is consistent for improved correlation using the combined model.

## 5.5 The detection of myocardial scar by ceMRI in patients with TnI positive chest pain and minimal angiographic coronary artery disease

CeMRI is able to both identify myocardial damage and describe its pattern. The aim of this analysis was to investigate the presence and pattern of DE in TnI positive patients with normal coronary arteries.

Of the 153 patients that entered the study, 80 (52%) were TnI positive. Of these TnI positive patients, 40 (50%) were diagnosed as STEMI and received prompt reperfusion therapy with IV thrombolysis. Forty (50%) were diagnosed with NSTEMI once the troponin result was available at 8-12 hours. Coronary angiography was performed at the discretion of the physician in charge of the patient's care and reported by the operator, independent to the study.

Coronary angiography was performed in 59/80 (74%) of all troponin positive patients which accounts for 32 (80%) of the STEMI group and 27 (68%) of NSTEMI group. No significant stenosis was detected in a total of 8 (14%) of angiograms performed (1 STEMI and 7 NSTEMI).

Of these 8 patients, mean (SD) 46 (12) years, 7 (88%) had evidence of DE. Four had the standard ischaemic distribution of DE involving the subendocardium (2 inferior, 1 lateral and 1 anterior). The infarct sizes were not trivial, median (IQR) infarct size was 8 (2.5-21) g and TnI was 22 (11 - 34) ng/ml.

**Figure 6-7** shows ceMRI images from three patients that had a normal coronary angiogram but were DE+. The left panel shows a SA image from a 54 year old female; the peak TnI was 14.5ng/ml, DE mass was 13g (13% LV mass) and LVEF was 49 %. There was inferior DE

that is transmural with an associated regional wall motion abnormality. The admission ECG showed 2 mm inferior ST depression and the coronary arteries were entirely normal and treatment prescribed was aspirin and statin.

The middle panel shows a ceMRI from a 66 year old male, peak TnI 29.3ng/ml, DE mass was 3.1 g (3% LV mass) and LVEF was 73%. Image shown is an adjusted LVOT view to incorporate the apical DE. Admission ECG showed significant ST depression and T wave inversion in leads V1 - V6 and III and aVF. Coronary angiography showed only plaque disease in the mid LAD (small vessel). There was a large dominant LCx and the RCA was a small vessel. Treatment was with aspirin, beta blocker, ACE inhibitor and statin. No embolic source identified at ceMRI. The most likely explanation was plaque rupture however this patient had had a MACE (stroke) by one year follow up.

The right panel shows a SA slice from a 31 year old male, peak TnI 49 ng/ml, DE mass 45.5 g (33% LV mass). The LVEF was 65% with lateral hypokinesia. There is transmural DE in the lateral position with MVO. Admission ECG showed deep anterior ST depression and the patient was thrombolysed at 102 minutes following onset of chest pain. Coronary angiography showed a 25-49% stenosis in the first obtuse marginal branch of the LCx, which is the likely culprit. No intervention was performed. Treatment was with aspirin, beta blocker, statin and ACE inhibitor. No MACE at three year follow up.

Three (2 male) patients had subendocardial sparing pattern of DE and were diagnosed with acute myocarditis. All three had normal coronary arteries. One patient was negative for DE

and had a TnI of 4.4 ng/ml and a final diagnosis of Takotsubo cardiomyopathy was made by the characteristic LV cinematographic images, **5.9 below**.

## 5.6 Serial assessment of MI size and characteristics using ceMRI

Fifty seven patients with first presentation single AMI defined by history, ECG, TnI and ceMRI were included in this study. Forty five (79%) attended for at least 2 studies, 35 (61%) for at least 3 studies and 25 (44%) for all 4.

Study 1 was performed at mean (SD) 2.6 (0.9) days, study 2 at 38 (16) days, study 3 at 203 (34) days and study 4 at 387 (33) days. The follow up scans were performed as near as possible to the predefined time points but tended to be later than the planned date. The standard deviations indicate that the actual scan dates are within 2 weeks at visit 2 and within a month at visits 3 and 4.

The clinical and angiographic characteristics of the study population are shown in **Table 5-11**. The majority of patients presented within 8 hours (upper IQR = 8.5 hours). Just over a half (58%) of infarcts were treated with IV thrombolysis at presentation. A further 19% had ST depression so would have been diagnosed based by STEMI equivalent criteria. Twenty three percent of patients had no ST deviation on the presenting ECG.

The clinical protocol at the time of the study did not include routine inpatient coronary angiography for post AMI patients, so it was only performed in 72%. If patients were clinically stable they could be discharged to have this performed as an outpatient. Subacute percutaneous intervention (PCI) is therefore defined as within 40 days of AMI and performed in 31 (54%) patients.

Table 5-11: Demographic and clinical characteristics of patients with single AMI

	Single AMI n=57
<i>Continuous variables</i>	
Age, years	60 (12)
BMI	26.9 (4)
TTMI risk score	3.5 (0.9)
Time from pain to MRI, hrs	63.6 (22.8)
Time from symptoms to admission, hrs	2.5 (1.6 – 8.5)
CRP, mg/dL	28.6 (10.2 - 57.4)
CK, IU/ml	736 (332 - 2136)
TnI, ng/ml	29.8 (11.4 - 64.9)
NtBNP 1, ng/L	1276 (740 - 2117)
NtBNP 3, ng/L	253 (131 - 540)
Presenting ECG total ST deviation, mm	10.3 (8.4)
Selvester score 1	3.9 (3.4)
Selvester score 2	4.2 (3.6)
<i>Categorical variables</i>	
Sex, male	43 (75)
Smoker	40 (70)
Family history	22 (39)
Diabetes	10 (18)
Hypertension	21 (37)
Hypercholesterolaemia	11 (19)
<i>Presenting ECG</i>	
ST elevation	27 (47)
ST depression	17 (30)
Acute reperfusion	33 (58)
<i>Cardiac catheterisation</i>	
Performed, n (%)	41 (72)
Subacute PCI	31 (54)
<i>Discharge Drugs</i>	
Aspirin	57 (100)
Beta blocker	49 (86)
ACE inhibitor	35 (61)
Statin	55 (98)

Data are presented as mean (SD) or median (IQR) for continuous variables and number (%) for categorical.

Table 5-12 shows the change in infarct size, characteristics and LV dimensions over 1 year. Mean infarct size and geometry all reduced over the time period and the greatest change occurred between visit 1 and visit 2. The most common infarct location seen at scan 1 was inferior in 27 (47%) patients. Anterior was seen in 17 (30%) patients and lateral in 13 (23%). At the follow up scans the distribution was more balanced.

Table 5-12: Change in infarct characteristics and LV dimensions over time

	Visit 1 n=57	Visit 2 n=42	Visit 3 n=37	Visit 4 n=30
Time chest pain to scan, days	2.6 (0.9)	38 (16)	203 (34)	387 (33)
<i>Infarct characteristics</i>				
Infarct size, g	34.6 (28.1)	24.9 (21.2)	26.9 (24.6)	24.8 (25.8)
Endocardial extent, °	92.3 (42.3)	82.7 (44.6)	80.2 (41.1)	63.9 (43.5)
Transmurality score	3.5 (0.8)	3.1 (0.8)	3.1 (0.8)	2.8 (0.9)
MVO early				
0	25 (44)	39 (93)	35 (95)	29 (97)
1	32 (66)	4 (9.5)	3 (8)	1 (3)
Size, g	9.2 (7.7)	4.0 (3.1)	2.2 (1.7)	5.7
MVO late				
0	36 (63)	40 (93)	37 (100)	30 (100)
1	21 (47)	3 (7)	0	0
Size, g	9.4 (6.7)	2.3 (1.3)	-	-
Infarct location				
Anterior	17 (30)	16 (38)	13 (35)	12 (40)
Inferior	27 (47)	16 (38)	16 (43)	12 (40)
Lateral	13 (23)	10 (24)	8 (22)	6 (20)
<i>LV dimensions</i>				
LVEF, %	55.9 (10.9)	56.9 (11.8)	54.8 (13.0)	57.6 (14.3)
LVEDV, ml	140.9 (37.6)	167.0 (50.9)	181.1 (59.1)	163.7 (55.8)
LVESV, ml	63.1 (25.5)	75.5 (40.8)	86.2 (55.4)	72.4 (48.1)
LV mass, g	130.4 (38.3)	145.2 (36.0)	138.3 (42.1)	150.6 (43.9)

Data expressed as mean (SD) or number (%) if categorical

Early MVO was present more frequently than late MVO (66 vs. 47%, p<0.0001). When late MVO is present there was always early MVO and 11 (20%) patients have early MVO only. The

mean (SD) values for early (18 (8) %) and late (16 (9) %) MVO size were also similar when expressed as a percentage of the infarct size. Passive diffusion of some contrast agent may reduce the MVO area during the excess time of > 8 minutes, particularly as in some patients early MVO has resolved altogether by 10 minutes. There was a marked drop off in the incidence of both early and late MVO between scan 1 and scan 2. However, in a minority of patients the MVO persisted **Figure 6-8**.

There were 25 patients with a complete set of data at all 4 time points. The mean (SD) infarct sizes in this group was 42 (36), 27 (25), 27 (28) and 25 (27) g at each respective time point. This represented a mean (SD) reduction of 15 (16) g (36%) between visits 1 and 2, 15 (14) g (36%) between visit 1 and visit 3 and 17 (16) g (40%) between visits 1 and visit 4. There was a greater absolute reduction in mean (SD) infarct size between visits 1 and 2 in those patients with late MVO, 23 (17) g, than those without, 6 (8) g,  $p=0.004$ .

When the whole group was considered using paired samples, there was a significant fall in infarct size between visits 1 and visit 2 and then the infarct sizes reached a plateau from visit 2 onwards ( $p<0.0001$ ) **Table 5-13**. This reduction was consistent in transmural extent. However endocardial extent seemed to continue to reduce over the four visits:  $-10^\circ$  between visit 1 and 2;  $-16^\circ$  between visits 1 and 3; and  $-30^\circ$  between visits 1 and 4. These differential patterns in change in infarct dimensions may merit further investigation in future studies.

The LVEF showed a trend to improving between visit 1 and visit 4 ( $p=0.07$ ). The structural measurements, LVEDV and LVESV, peaked at 6 months. At 1 year there was a reduction back towards the baseline measurements. This may have been due to the beneficial effects of



secondary prevention (beta blocker and ACE I) as the doses are uptitrated and anti-remodelling occurs.

LV mass returned almost to baseline at visit 3 and then compensatory hypertrophy may be seen at visit 4.

**Table 5-13: Change in selected ceMRI characteristics with time for all patients**

	$\Delta V2 - V1$ (95% CI)	$\Delta V3 - V1$ (95% CI)	$\Delta V4 - V1$ (95% CI)	P
<i>Infarct characteristics</i>				
Infarct size, g	-12.7 (-16.1, -9.3)	-13.0 (-16.5, -9.4)	-14.1 (-18.0, -10.2)	<0.0001
Endocardial extent, °	-10.2 (-19.1, -1.4)	-16.5 (-26.0, -7.0)	-30.8 (-41.1, -20.5)	<0.0001
Transmurality score	-0.3 (-0.6, -0.05)	-0.4 (-0.7, -0.1)	-0.7 (-1.0, -0.4)	<0.0001
<i>LV dimensions</i>				
LVEF, %	2.1 (-0.3, 4.4)	1.2 (-1.3, 3.7)	3.5 (0.8,6.2)	0.07
LVEDV, ml	23.0 (12.5, 33.4)	30.8 (19.9, 41.8)	18.8 (6.8, 30.7)	<0.0001
LVESV, ml	10.0 (2.1, 17.9)	15.9 (7.6, 24.2)	5.3 (-3.7, 14.3)	0.0019
LV mass, g	11.4 (4.4, 18.3)	0.6 (-6.7, 7.9)	15.2 (7.3, 23.2)	0.00011

Date expressed as mean difference and confidence intervals. Visit 1 is the baseline and used as the reference.  
V, visit.

In order to investigate potential factors involved in different healing rates, MVO (early and late), acute reperfusion status and subacute PCI were assessed **Table 5-14** and **Figure 5-7**.

There was no difference in rate of reduction in infarct size between the 2 subacute PCI groups.

This result is likely to be related to the large variation in time points at which PCI was performed between visit 1 and visit 2. The data is expressed as mean difference with 95% confidence intervals between the groups (data not shown).

Table 5-14: The influence of MVO and acute reperfusion status on the healing rates of myocardial infarction

		$\Delta V2 - V1$ (95% CI)	$\Delta V3 - V1$ (95% CI)	$\Delta V4 - V1$ (95% CI)	P
<i>Infarct size</i>	MVO early	-11.9 (-18.4, -5.3)	-8.2 (-15.2, -1.3)	-9.2 (-17.1, -1.4)	0.0036
	MVO late	-15.7 (-21.8, -9.7)	-12.1 (-18.3, -5.8)	-15.0 (-21.8, -8.2)	<0.0001
	Reperfusion	-5.5 (-12.2, 1.3)	-5.5 (12.7, 1.8)	-9.6 (17.4, -1.8)	0.095
<i>LVEF</i>	MVO early	-3.01 (-7.8, 1.7)	-4.0 (-9.1, 1.1)	-6.3 (-12.0, -0.6)	0.15
	MVO late	-2.2 (-7.0, 2.5)	-4.2 (-9.1, 0.8)	-6.0 (-11.3, -0.6)	0.14
	Reperfusion	-3.4 (-8.1, 1.4)	-4.8 (-9.9, 0.3)	0.43 (-5.1, 6.0)	0.16
<i>LVEDV</i>	MVO early	9.1 (-12.24, 30.5)	5.2 (-17.6, 28.0)	1.8 (-24.0, 27.7)	0.85
	MVO late	22.4 (1.8, 42.9)	30.8 (9.4, 52.2)	26.8 (3.6, 50.1)	0.022
	Reperfusion	6.81 (-14.7, 28.3)	9.0 (-14.0, 32.1)	11.2 (-13.7, 36.1)	0.79
<i>LVESV</i>	MVO early	10.5 (-5.5, 26.4)	13.8 (-3.2, 30.8)	12.8 (-6.5, 32.1)	0.34
	MVO late	17.3 (2.1, 32.6)	27.6 (11.8, 43.5)	25.9 (8.6, 43.1)	0.0029
	Reperfusion	12.68 (-3.4, 28.7)	17.0 (-0.15, 34.2)	10.6 (-7.9, 29.2)	0.22
<i>LV mass</i>	MVO early	3.8 (-10.2, 17.8)	-13.5 (-28.4, 1.5)	-7.7 (-24.7, 9.2)	0.13
	MVO late	0.13 (-14.0, 14.2)	-12.0 (-26.7, 2.7)	1.0 (-15.0, 17)	0.29
	Reperfusion	-9.6 (-23.9, 4.7)	-1.6 (-16.9, 13.8)	-7.7 (-24.3, -1.8)	0.53

Data expressed as mean difference between groups with confidence intervals.

The rate of change in infarct size is greater in those patients with both early (p=0.0036) and late (p<0.0001) MVO than those without. There is a trend to a greater reduction in infarct size in the reperfusion vs. non reperfusion groups (p=0.095). Patients with late MVO demonstrate significant increases in LV dimensions; LVEDV (mean gain 27ml, p=0.022) and LVESV (mean gain 26ml, p=0.0029) than those without late MVO.

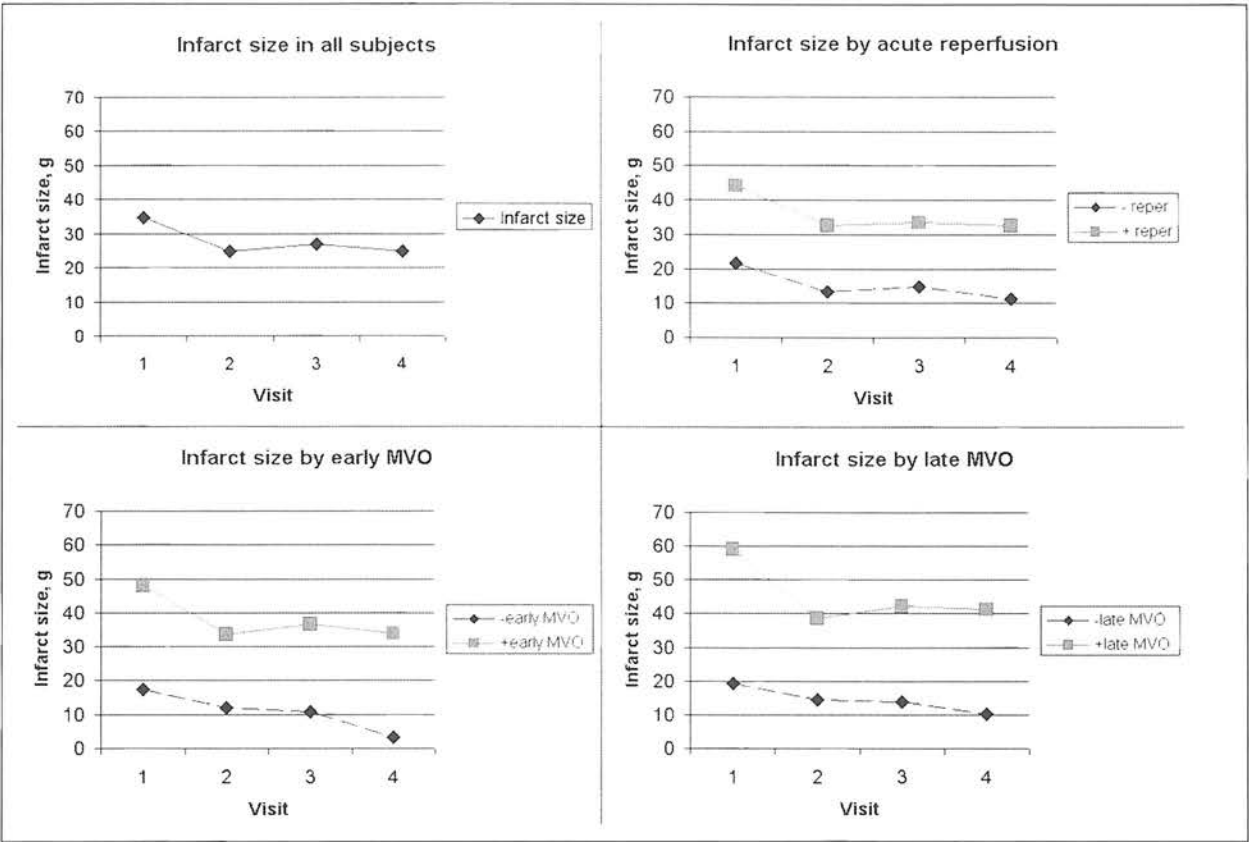


Figure 5-7: Change in infarct size over time

Figure 5-7 illustrates the different gradients for reduction of infarct size between visit 1 and visit 2 for the total group and for each of the subgroups. In all cases the group with the larger infarcts had a steeper gradient.

## 5.7 Usefulness of CRP in detecting higher risk patterns of AMI defined by ceMRI

This section uses ceMRI to describe the role of inflammation in ACS as measured by CRP.

The diagnostic ability of CRP in patients admitted to hospital to rule out MI is tested and then correlated with infarct size. The ceMRI findings at the previously investigated CRP cut off levels,  $>3$  and  $>10$  mg/L, shown to be associated with adverse outcome are described. Finally the potential role of CRP in the detection of infarcts associated with microvascular obstruction is assessed and a new cut off level presented.

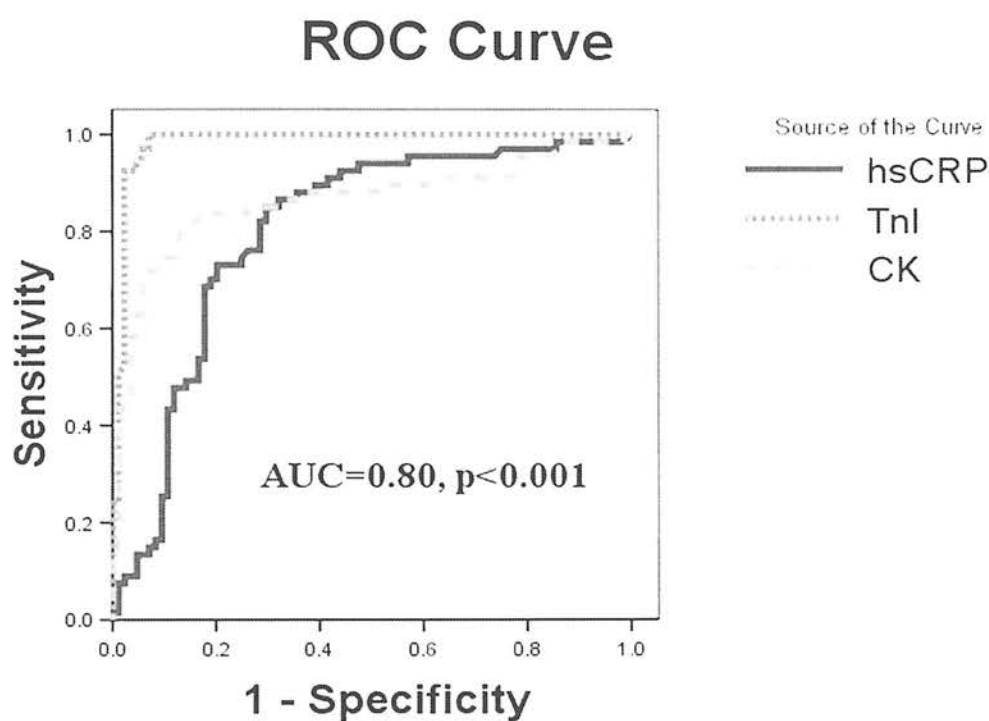
Seventy one (46%) of the patients admitted to rule out AMI had CRP  $> 10$ mg/L **Table 5-15** and they had a higher mean WCC ( $10.5$  vs.  $7.3 \times 10^9/L$ ,  $p<0.001$ ). Patients with a high CRP were older (mean 58 vs. 54 years,  $p=0.05$ ) and had lower systolic (mean 122 vs. 129 mmHg,  $p=0.03$ ) and diastolic (mean 74 vs. 81 mmHg,  $p<0.001$ ) blood pressures. They had a larger median AMI size by CK, TnI and ceMRI. LVEF was lower during admission (57 vs. 65 %,  $p<0.001$ ) and at 6 months follow up (56 vs. 66 %,  $p<0.001$ ). More patients had ST elevation (38 vs. 11 %,  $p<0.001$ ) and ST depression (25 vs. 10 %,  $p=0.01$ ) on the presenting ECG. More patients had DE (80 vs. 35 %,  $p<0.001$ ). The prescription rates of secondary prevention drugs reflected the higher rate of AMI with more patients receiving a beta blocker, ACE inhibitor and statin in the high CRP group. Amongst those patients with CRP  $<10$ mg/L a greater proportion had unstable angina (24 vs. 4 %,  $p=0.044$ ) and non cardiac chest pain (36 vs. 11 %,  $p<0.001$ ). Patients with a low CRP were more likely to have either a family history of cardiovascular disease or a past medical history of hypercholesterolaemia.

Table 5-15: Demographic and clinical characteristics for whole population and according to CRP

	Total (n=153)	CRP <10 (n=80)	CRP >10 (n=71)	p value
<i>Continuous variables</i>				
Age, years	56.3 (12.8)	54.3 (12.0)	58.4 (13.4)	0.05
Systolic BP	125.6 (19.7)	129.0 (19.4)	122.1 (19.8)	0.03
Diastolic BP	77 (12.8)	80.8 (12.4)	73.6 (12.4)	<0.001
BMI	27.0 (4.7)	26.4 (4.3)	27.6 (5.1)	0.107
TIMI risk score	2.6 (1.2)	2.1 (1.2)	3.2 (1.2)	<0.001
Time from pain to MRI, hrs	54.7 (32.0)	50.7 (37.3)	59 (24.6)	0.108
Median (IQR) infarct size, g	-	0 (0-6.1)	27 (1-46.1)	<0.001
Median (IQR) CRP, mg/dL	7.3 (1.8-36.4)	2.0 (1.1-4.2)	38.0 (23.3-83.8)	<0.001
Median (IQR) WCC, $\times 10^9/l$	8.6 (7.1-11.2)	7.3 (6.5-9.0)	10.5 (8.3-13.7)	<0.001
Median (IQR) CK, IU/ml	-	117 (77-203)	504 (165-2057)	<0.001
Median (IQR) TnI, ng/ml	-	0 (0-0.85)	23.6 (2.2-60)	<0.001
LVEF 1, %	60.8 (11.6)	64.5 (8.6)	56.5 (13.0)	<0.001
LVEF 3, %	61.5 (12.4)	66.1 (7.9)	56.4 (14.2)	<0.001
<i>Categorical variables</i>				
Smoker	103 (67)	50 (62.5)	51 (71.8)	0.22
Family history	70 (46)	43 (53.7)	25 (35.2)	0.02
Diabetes	38 (25)	21 (26.2)	17 (23.9)	0.46
Hypertension	53 (35)	24 (30.0)	28 (39.4)	0.22
Hypercholesterolaemia	33 (22)	22 (27.5)	10 (14.0)	0.04
<i>Admission ECG:</i>				
ST elevation	37 (24)	9 (11.3)	27 (38.0)	<0.001
ST depression	26 (17)	8 (10.0)	18 (25.3)	0.01
<i>Discharge diagnosis</i>				
DE +	85 (56)	28 (35.0)	57 (80.3)	<0.001
Single acute MI	57 (37)	14 (17.5)	43 (60.1)	<0.001
Acute and prior MI	11 (7.1)	3 (3.8)	7 (9.9)	0.19
Minimal myocyte necrosis	9 (5)	6 (7.5)	3 (4.2)	0.40
Unstable angina	11 (7)	9 (11.4)	2 (3.1)	0.044
Acute myocarditis	3 (2)	1 (1.3)	2 (2.8)	0.60
Prior non-ischaemic fibrosis	5 (3)	3 (3.8)	2 (2.8)	0.75
Prior MI	9 (5.8)	7 (8.8)	2 (2.8)	0.174
Chest pain, other	48 (31.3)	39 (48.8)	9 (12.7)	<0.001
<i>Discharge Drugs:</i>				
Aspirin	91 (59)	43 (53.8)	47 (66.2)	0.12
Beta blocker	91 (48.0)	32 (40.0)	41 (57.7)	0.03
ACE inhibitor	40 (26.3)	11 (13.8)	29 (40.8)	<0.001
Statin	69 (45.2)	26 (36.3)	42 (59.2)	0.001

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Comparisons made between the 2 groups reperfusion and non reperfusion. Two sample t-test used to compare continuous variables and chi-squared test for categorical. Wilcoxon rank sum or Mann-Whitney U test used for non-normal data. Data from 2 patients is omitted from the total population due to missing CRP values. ACE, angiotensin converting enzyme; BMI, body mass index; CRP, C-reactive protein; DE+, ceMRI positive for delayed hyperenhancement; TIMI, thrombolysis in myocardial infarction; WCC, white cell count.

To test the ability of CRP to diagnose AMI using a ceMRI gold standard for infarct presence, Receiver Operator Characteristics (ROC) were assessed in all 153 patients. The area under the curve (AUC) (95% CI) for CRP was 0.8 (0.73, 0.87),  $p<0.001$  **Figure 5-8**. For reference, the ROC curves for TnI (AUC 0.98 (0.96, 1.00)) and CK (AUC 0.86 (0.79, 0.93)) are also shown. The AUC of CRP compares favourably with both of these established markers of myocardial necrosis.



**Figure 5-8: Receiver Operator Characteristics for CRP, TnI and CK using ceMRI gold standard**

Of the 57 patients with single AMI, 43 (75%) had a CRP >10 but there was no difference in WCC (11.4 vs. 9.6,  $p=0.109$ ) **Table 5-16**.

These patients had significantly larger infarct sizes by ceMRI both acutely (median 40 vs. 14 g,  $p=0.001$ ) and at follow up (28.0 vs. 7.7 g,  $p=0.009$ ). The endocardial extent was greater (99° vs. 66°,  $p=0.02$ ) but there was no difference in transmural extent.

They showed a trend to reduced mean LV ejection fraction during admission (54 vs. 61 %,  $p=0.07$ ) that reached significance at 6 months (53 vs. 63%,  $p=0.001$ ). The admission LVESV was higher (67 vs. 51 ml,  $p=0.005$ ) but this difference was no longer significant at 6 months. ST deviation occurred more frequently on the admission ECG in the high CRP group but this difference did not reach significance.

The prevalence of late MVO in the total population is just over a quarter at 26%. Patients with a high CRP had a greater proportion of early MVO (70% vs. 29%,  $p=0.011$ ) and late MVO (47% vs. 7%,  $p=0.01$ ).

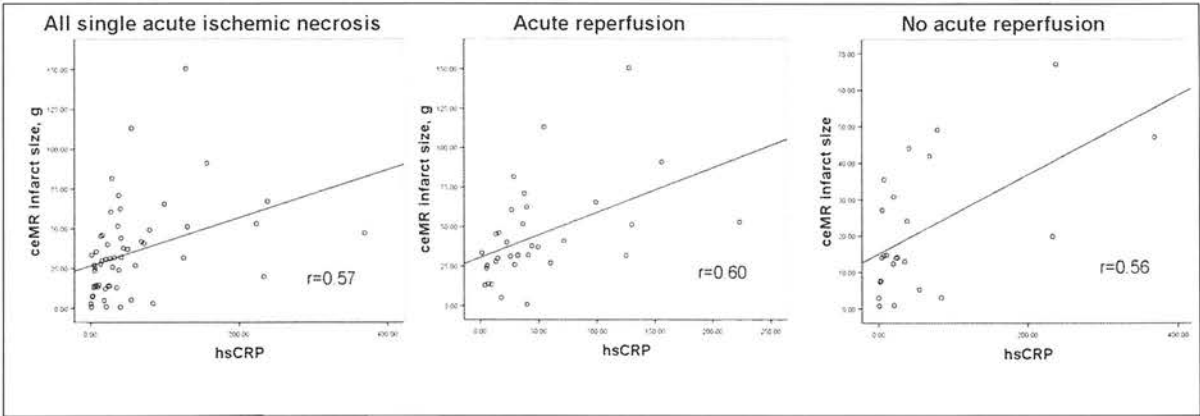
Table 5-16: CeMRI, biochemical and electrocardiographic characteristics in patients with single AMI according to CRP

	Total (n=57)	CRP<10 (n=14)	CRP>10 (n=43)	p value
<b>Infarct characteristics</b>				
<i>Continuous variables</i>				
Median (IQR) Acute infarct size, g	31.2 (14.4-48.2)	14.2 (7.7-25.7)	40.1 (21.8-67.2)	0.001
Median (IQR) Final infarct size, g	22.2 (6.3-38.8)	7.7 (4.0 – 22.2)	28.0 (15.6-40.6)	0.009
Transmurality score	3.5 (0.8)	3.1 (1.0)	3.6 (0.73)	0.15
Endocardial extent	90.7 (43.9)	66.4 (36.6)	98.9 (43.5)	0.02
<i>Categorical variables</i>				
MVO early	35 (61)	4 (29)	30 (70)	0.011
MVO late	22 (39)	1 (7)	20 (47)	0.01
Transmurality $\geq 3$	44 (77)	9 (64)	35 (81)	0.185
<b>LV structure and function</b>				
LVEF 1,%	55.9 (10.9)	60.5 (7.5))	54.4 (11.5)	0.07
LVEF 3, %	54.8 (13.0)	63.4 (3.9)	52.8 (13.5)	0.001
LVEDV 1, ml	140.9 (37.6)	130.4 (28.2)	144.3 (39.9)	0.234
LVEDV 3, ml	181.1 (59.1)	152.7 (39.3)	187.5 (61.4)	0.16
LVESV 1, ml	63.2 (25.3)	51.3 (12.7)	67.0 (27.5)	0.005
LVESV 3,ml	86.0 (54.8)	55.5 (15.9)	93.1 (59.0)	0.106
LV mass 1, g	130.4 (38.3)	119.7 (37.3)	133.8 (38.4)	0.23
LV mass 3, g	138.3 (42.1)	117.5 (25.5)	143.1 (43.9)	0.15
<b>Biochemical markers</b>				
Median (IQR)WCC,x10 <sup>9</sup> /l	10.9 (8.7-13.8)	9.6 (8.7-11.6)	11.4 (8.7-14.0)	0.109
Median (IQR) TnI, ng/ml	29.8 (11.4-64.9)	11.3 (4.4-36.2)	41.7 (20.2-29.0)	0.005
<b>Admission ECG</b>				
ST elevation	27 (47)	5 (36)	22 (51)	0.32
ST depression	17 (30)	4 (29)	13 (30)	0.91

All available data used; n is the maximum number in each group. Data are presented as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Two sample t-test used to compare continuous variables and chi-squared test for categorical. Wilcoxon rank sum test used for non-normal data. Infarct size represents planimetered delayed enhancement (DE) mass  
Abbreviations as previous tables.



Having established that the diagnostic ability of CRP compares favourably with standard biomarkers the correlation of CRP with infarct size was assessed **Figure 5-9** and **Table 5-17**.



**Figure 5-9: Correlations CRP and infarct size by ceMRI for all infarcts and by reperfusion status**

There is a moderate correlation of CRP with infarct size in the total group ( $r=0.57$ ,  $p<0.001$ ), in the reperfused group ( $r=0.6$ ,  $p<0.001$ ) and in the non-reperfused group ( $r=0.56$ ,  $p=0.004$ ). When CRP was compared to final infarct size (mean 38 days) in the non-reperfused group there was a significant increase in the correlation ( $r=0.56$  up to  $0.87$ ,  $p=0.04$ ).

The WCC mildly correlates with infarct size ( $r=0.37$ ,  $p=0.004$ ) in the total population. In contrast to the standard biomarkers (CK, TnI) WCC correlates better with non-reperfused acute myocardial infarct size ( $r=0.55$  vs.  $r=0.20$ ,  $p=0.14$ ). Similarly, only in the non-reperfused group did CRP correlate with TnI ( $r=0.73$ ,  $p<0.001$ ).

There was a modest correlation between CRP and acute LVEF in the reperfused group ( $r=-0.49$ ,  $p=0.004$ ) which improved when compared to the 6 month LVEF ( $r=-0.67$ ,  $p<0.001$ ).

Table 5-17: Selected correlations with CRP by acute reperfusion status

Comparisons	All cases		Reperfusion		No reperfusion	
	r	p	r	p	r	p
<i>Acute Infarct</i>						
CRP v Infarct size, g	0.57 (n=57)	<0.001	0.60 (n=33)	<0.001	0.56 (n=24)	0.004
TnI v Infarct size, g	0.69 (n=47)	<0.001	0.70 (n=26)	<0.001	0.43 (n=21)	0.05
WCC v infarct size, g	0.37 (n=57)	0.004	0.20 (n=33)	0.27	0.55 (n=24)	0.006
CRP v TnI (ng/ml)	0.41 (n=47)	<0.001	0.23 (n=26)	0.25	0.73 (n=21)	<0.001
CRP v LVEF, %	-0.28 (n=57)	<0.001	-0.49 (n=33)	0.004	-0.12 (n=24)	0.96
<i>Chronic Infarct</i>						
CRP v Infarct size, g	0.56 (n=43)	<0.001	0.40 (n=26)	0.05	0.87 (n=17)	<0.001
CRP v LVEF, %	-0.63 (n=38)	<0.001	-0.67 (n=25)	<0.001	-0.40 (n=13)	0.17

All available data used. Data are presented by number (n) suitable for analysis, Spearman’s rank correlation coefficient (r) and significance (p).

CRP, C-Reactive Protein; TnI, troponin I; WCC, white cell count; LVEF, left ventricular ejection fraction.

The diagnostic abilities of the available biochemical and bioelectrical markers to determine presence of late MVO were then tested and the ROC curve is shown **Figure 5-10**. The ROC curves for early MVO were similar although AUC reduced for each parameter, not shown.

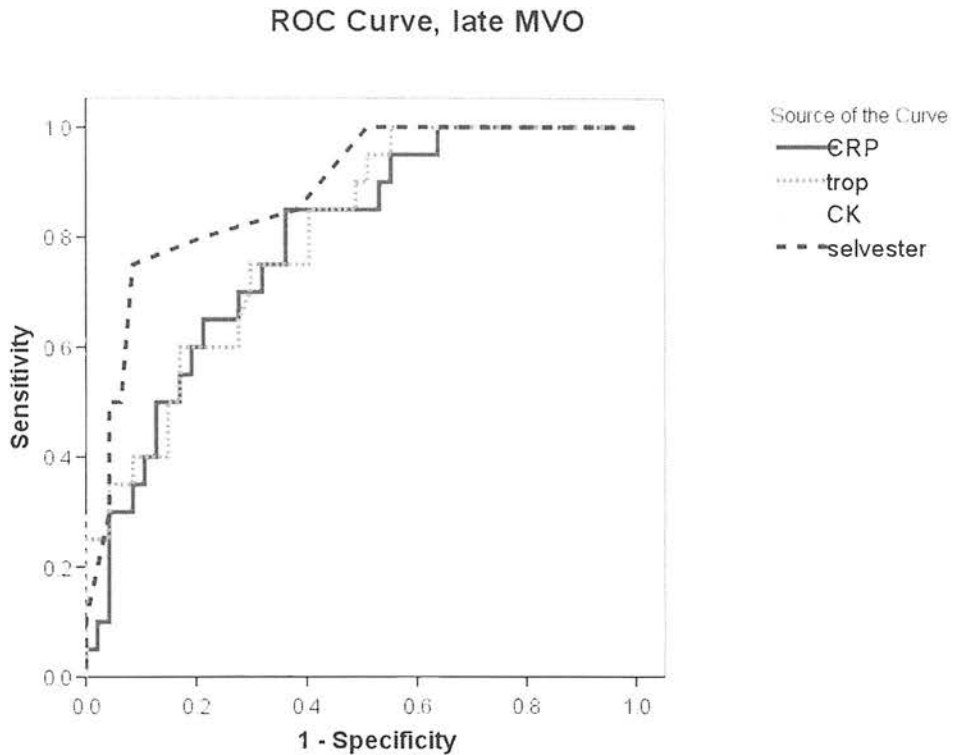


Figure 5-10: Receiver Operator Characteristics for CRP, Troponin, CK and the Selvester score for the prediction of late MVO

Surprisingly the “old fashioned” CK comes out on top with an AUC of 0.93 (0.87 - 0.99) with the Selvester score next, AUC 0.88 (0.79 – 0.96). Troponin (0.79 (0.69 – 0.9)) and CRP (0.79 (0.68 – 0.9)) are very similar **Table 5-18** and **Figure 5-10**.

**Table 5-18: Area under the curve and ROC determined optimum sensitivity and specificity of routine biochemical and bioelectrical markers of myocardial infarction in the diagnosis of late MVO**

	AUC (95% CI)	p	Cut off	Sens. (95% CI)	Spec. (95% CI)	PPV	NPV	LR
CRP	0.79 (0.68-0.9)	<0.0001	> 26	0.85 (0.76-0.95)	0.66 (0.56-0.75)	0.47	0.92	2.5
TnI	0.79 (0.69-0.9)	<0.0001	> 25	0.85 (0.76-0.95)	0.62 (0.53-0.72)	0.45	0.92	2.3
CK	0.93 (0.87-0.99)	<0.0001	> 850	0.90 (0.80-1.0)	0.80 (0.70-0.89)	0.61	0.96	4.4
ECG (SS)	0.88 (0.79-0.96)	<0.0001	> 3.5	0.75 (0.64-0.86)	0.80 (0.69-0.91)	0.63	0.88	3.8

The cut off values are the optimum from the coordinates of the ROC curve.  
AUC, Area under the curve; CI, confidence interval; ECG, represents the Selvester score; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio. Prevalence of late MVO in the population is 0.26.

Using the coordinates of the ROC curve the cut off points with optimum sensitivity and specificity in the diagnosis of late MVO were defined. A CRP of >26 mg/L has a sensitivity and specificity of 0.85 and 0.66 respectively, with a likelihood ratio of 2.5. A similar result is obtained using a TnI cut off of >25ng/ml. The ECG derived Selvester score as a measure of infarct size has a cut off of >3.5 points. The sensitivity is 0.75 and specificity 0.8 and likelihood ratio of 3.8.

The most useful test in determining presence/ absence of MVO in this population is CK with a sensitivity of 0.9 and specificity of 0.8 at a cutoff point of >850 IU/ ml (peak value out of 3 (admission, 12 hours and mean 2.6 days)).

A model was constructed using logistic regression, (method: forward stepwise (likelihood ratio)) to look for the best parameters in the detection of late MVO. In addition to the above 4 biomarkers, the model included age and time from chest pain to presentation.

Table 5-19: Logistic regression to predict presence of late MVO

		Wald	p	Exp B (95% CI)
Step 1	CK	18.5	<0.0001	1.002 (1.001-1.003)
Step 2	CRP	6.70	0.01	1.013 (1.003-1.024)
Step 3	CK	14.8	<0.0001	1.002 (1.001-1.004)
	CRP	6.3	0.012	1.014 (1.003-1.025)
	CK	9.1	0.003	1.002 (1.001-1.003)
	Selvester	3.3	0.07	1.4 (0.97-2.021)

Variables entered on step 1, CK, step 2, CRP, step 3, Selvester. Variables not in the equation: TnI, age, time from chest pain to admission.

The only 3 variables left in the model were CK, CRP and Selvester **Table 5-19**. CK was the strongest predictor with overall 86% of late MVO correctly predicted, rising to 88.1% with the addition of CRP and 90% when all 3 are present.

It is slightly surprising that TnI does not feature but it may be that CK provides enough information about necrotic myocytes and the additional information from CRP relates to an additional inflammatory response that may be associated with MVO.

To investigate reasons why CRP infers increased risk, the ability to predict MVO at each routinely used CRP cut off was tested for both early and late MVO in TnI positive patients.

The sensitivities and specificities of CRP to detect early MVO were: CRP>3 =0.97 (0.86, 1.0) and 0.25 (0.14, 0.36), LR 1.3; CRP >10 =0.87 (0.76, 0.98) and 0.45 (0.34, 0.56), LR 1.6; and CRP >26 =0.67 (0.56, 0.78) and 0.7 (0.59, 0.81), LR 2.2.

**Table 5-20** shows the results for late MVO. There were no patients with late MVO that had a CRP <3 and only 1 patient <10 mg/L. This is reflected in the high sensitivity but low

specificity. The lower limit of the confidence interval for specificity is >0.5 for early and late MVO at a CRP of >26mg/L.

**Table 5-20: Sensitivity and specificity of CRP in the diagnosis of late MVO by ceMRI in TnI positive patients**

		Late MVO by ceMRI		Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value	Negative predictive value	Likelihood ratio
		Yes (n=21)	No (n=58)					
CRP>3	Yes (n=68)	21	47	1.0 (0.9-1.0)	0.19 (0.09-0.29)	0.3	1.0	1.2
	No (n=11)	0	11					
CRP>10	Yes (n=55)	20	35	0.95 (0.85-1.0)	0.40 (0.30-0.49)	0.36	0.96	1.6
	No (n=24)	1	23					
CRP>26	Yes (n=38)	18	20	0.86 (0.76-0.95)	0.66 (0.56-0.75)	0.47	0.92	2.5
	No (n=41)	3	38					

There were 3 patients with late MVO but CRP <26 mg/L (CRP values 7.33 (male, age 54), 13.38 (male, age 31) and 16.0 (female, age 40); in all cases the CK was >850, the TnI > 25 and all were transmural (score 4). Two were thrombolysed and the Selvester score was 5 in both.

**Figure 6-9** shows a SA slice from each patient demonstrating late MVO.

On the left is a patient that had a lateral infarct (36g), 12% of which was MVO.

The patient with the anterior MI (46g) had an admission LVEF of 48%, 10% of which was MVO, middle panel.

The 31 year old had 45g of lateral infarction, 10% of which was MVO, a normal LVEF and Selvester score of 1, right panel. He had minimal coronary disease at angiography so plaque rupture was thought to be the aetiology (Intravascular Ultrasound (IVUS) was not performed).

There is no obvious explanation as to why these patients had late MVO and lower CRP although the ratio of MVO/ infarct size for all three is in the lower half (the median ratio being 13%).

## 5.8 MMP-1 promoter polymorphisms and changes in LV volume following AMI

Changes in LV volumes in patients with differing MMP-1 genotypes are listed in **Table 5-21**.

In comparison with patients with the G/G genotype, patients possessing a single GG allele exhibited no difference in volume changes after AMI.

**Table 5-21: Clinical and ceMRI parameters in patients with differing MMP-1 genotypes**

Characteristics	All Patients (n = 42)	G/G Genotype (n = 11)	G/GG Genotype (n = 25)	GG/GG Genotype (n = 6)	p Value
Age (yrs)	60 (45–67)	63 (52–70)	61 (45–66)	52 (42–71)	0.66
Men	34 (81%)	10 (91%)	18 (72%)	6 (100%)	0.18
Hypertension	15 (36%)	4 (36%)	9 (36%)	2 (33%)	0.97
Diabetes mellitus	4 (10%)	—	3 (12%)	1 (17%)	0.63
Hypercholesterolemia*	24 (57%)	6 (55%)	13 (52%)	5 (83%)	0.37
Current smoker	33 (79%)	8 (73%)	21 (84%)	4 (67%)	0.95
Anterior myocardial infarction†	13 (31%)	6 (55%)	7 (28%)	—	0.08
Inferior/lateral myocardial infarction†	26 (62%)	5 (45%)	15 (60%)	6 (100%)	0.08
ST-elevation myocardial infarction	19 (45%)	4 (36%)	12 (48%)	3 (50%)	0.79
12-h cardiac troponin I (ng/ml)	46 (9–78)	38 (10–86)	55 (7–94)	30 (1–72)	0.72
Revascularization during study period‡	23 (55%)	7 (64%)	12 (48%)	4 (67%)	0.56
Discharge medication					
ACE inhibitor or ARB	28 (67%)	8 (73%)	16 (64%)	4 (67%)	0.88
β blocker	34 (81%)	9 (82%)	19 (76%)	6 (100%)	0.40
MRI measurements at baseline					
LV end-systolic volume (ml)	61 (49–79)	75 (56–94)	60 (48–76)	54 (32–65)	0.16
LV end-diastolic volume (ml)	146 (120–174)	154 (140–197)	145 (120–170)	122 (103–155)	0.19
LV ejection fraction (%)	58 (49–65)	54 (39–60)	59 (50–65)	62 (46–67)	0.52
Infarct size (g)	30 (8–46)	24 (6–70)	30 (11–47)	31 (6–66)	0.98
MRI measurements at 6 mo					
LV end-systolic volume (ml)	72 (52–100)	73 (63–108)	68 (36–101)	71 (48–100)	0.72
LV end-diastolic volume (ml)	166 (132–205)	165 (143–204)	166 (127–205)	176 (140–236)	0.84
LV ejection fraction (%)	58 (49–65)	55 (46–62)	57 (52–69)	64 (46–68)	0.35
Changes in LV volumes					
Change in end-systolic volume (ml)	8 (–7 to 21)	7 (–6 to 14)	3 (–15 to 24)	16 (12–42)	0.16
Change in end-diastolic volume (ml)	20 (–10 to 51)	7 (–13 to 32)	10 (–11 to 54)	52 (35–85)	0.07
% change in end-systolic volume	14 (–17 to 41)	13 (–8 to 19)	4 (–23 to 42)	45 (23–70)	0.05
% change in end-diastolic volume	11 (–8 to 39)	4 (–10 to 18)	8 (–9 to 37)	41 (28–70)	0.03

Results shown are medians (interquartile ranges) or absolute values (percentages).  
 \*History of hypercholesterolemia or random cholesterol >5.5 mmol/L (212 mg/dl) on admission.  
 †In 3 cases, the site of infarction could not be accurately defined.  
 ‡Seventeen during index admission, 6 during subsequent 6 months.  
 ACE = angiotensin converting enzyme; ARB = angiotensin-II receptor antagonist.

Similarly, there was no difference in allele frequency in patients exhibiting a  $\leq 10\%$  or  $> 10\%$  increase in LV volumes **Table 5-22**. However, patients possessing the GG/GG MMP-1



genotype were significantly more likely to experience a >10% increase in LV end-systolic volume (p = 0.02, relative risk 1.4, 95% CI 1.1 to 1.8) or LV end-diastolic volume (p = 0.009, relative risk 1.4, 95% CI 1.1 to 1.9) compared with those with the G/G or G/GG genotype.

**Table 5-22: MMP-1 Allele frequencies in patients exhibiting ≤ 10% or > 10% increase in LV volumes after an AMI**

	G Allele	GG Allele	Relative Risk (95% CI)	p Value
≤10% increase in LVESV	24	14		
>10% increase in LVESV	23	23	1.26 (0.87–1.84)	0.27
≤10% increase in LVEDV	27	15		
>10% increase in LVEDV	20	22	1.35 (0.91–1.99)	0.19

CI = confidence interval; LVEDV = LV end-diastolic volume; LVESV = LV end-systolic volume.

### 5.9 Additional ceMRI findings in patients with first hospital admission for chest pain to rule out MI

This section describes additional findings in patients admitted to rule out MI and is based on the diagnostic category **Figure 5-4**. The chapter also includes a description of patients from the whole population with right ventricular infarction or LV thrombus

#### Acute Myocarditis

Three patients were diagnosed with acute myocarditis based on a rise and fall of TnI, normal coronary angiography and a subendocardial pattern of DE that did not adhere to a particular coronary artery territory.

Table 5-23: Selected clinical features of patients with discharge diagnosis of acute myocarditis

No.	Age	Sex	ECG	TnI	CRP	WCC	Nt-BNP	DE, g	LVEF %	TIMI
37	34	M	Inf STE	70.9	107	10.3	2454	74.7	53	3
70	37	F	Norm	0.4	1.5	8.6	333	6.3	61	2
229	42	F	Lat. STE	29.3	259	16.5	4225	36.5	46	3

No., patient number, DE, Delayed enhancement; Nt-BNP, N terminal Brain Natriuretic Peptide; STE, ST segment elevation

Two patients presented with ST elevation and were considered for acute reperfusion therapy. One (number 37) received thrombolysis **Figure 6-10** and the intention for the other was primary PCI.

The 3rd patient's presenting ECG was normal. The biomarkers of myocardial necrosis (TnI, CK) and inflammatory markers (CRP, WCC) levels were variable and greater in the two patients with largest DE mass. The TIMI score was low or low/moderate risk in all. Points were scored for chest pain, positive biomarkers and ECG changes. None of the patients had  $\geq 3$  traditional risk factors and only one smoked. All 3 patients underwent diagnostic coronary angiography and no significant stenosis was identified. The working clinical diagnosis was, "coronary embolus/ spasm" until ceMRI was performed. Delayed hyperenhancement that spares the subendocardium and does not match a coronary artery territory is demonstrated (**Figure 6-10**, upper left: 4 chamber and upper right: mid ventricular SA).

It was possible to planimeter the regions of hyperenhancement in all patients and the % LV mass was variable. No regional wall motion abnormality was detected and all were reported as having normal LV function by echo. By ceMRI the LV ejection fraction varied between 46 and 61%. By 28 days the LVEF was  $>60\%$  in all three cases and remained so out to one year. Two patients (numbers 37 and 70) attended for one year follow up and the DE mass was reduced (74.7g to 48.9g and 6.3g to 2.3g). The third patient only attended for 28 day follow up and again DE mass was reduced (36.5g to 6.3g).

One patient (number 37) was treated with ACE inhibitor, aspirin and B blocker whilst the other two were maintained on aspirin only. NtBNP was elevated in all three patients during admission (2454, 333 and 4225) falling to near normal levels (305, 23.2 and 339) by 28 days. Values were within normal limits in the two patients that attended for 1 year follow up (18 and 26). **Figure 6-11** shows the SA and 4 chamber views at each follow up scan of the index

patient illustrating the persistence of, but reduction in, area of DE over time (scan 1, 74.7g; scan 2, 70g; scan 3, 45.7g; and scan 4, 48.9g).

### **Prior myocardial infarction**

Twenty (13%) patients had evidence of previous myocardial infarction when examined using ceMRI; 11 were TnI positive and nine were TnI negative.

### **Troponin I positive patients**

Eleven patients with a mean (SD) age 62 (13) years, 7 (64%) of whom were male were TnI positive (median (IQR) 10 (7-25)) with an ischaemic pattern of DE in  $\geq 2$  coronary artery territories and/ or evidence of prior myocardial infarction on the presenting ECG (Q waves)

### **Figure 6-12.**

Three patients presented with ST elevation and were thrombolysed; two had significant ST depression. Mean (SD) LVEF was 56.6 (11.3) % and similar to the acute single MI group.

Three patients had prior infarction by ECG criteria but single region of DE suggesting that the time period from infarct to patient presentation was longer than represented by the patient's symptoms, but within 2 weeks as TnI was still detectable. The location of the Q waves matched the DE location by ceMRI (two inferior and one anterior) in three out of four cases. Seven (64%) patients had a mean transmural score of  $\geq 3$ .

Early MVO resolves with time in the majority of cases so its presence may help to differentiate between acute and prior MI. Four patients had early MVO in 1 of the infarct areas. Two patients (numbers 149, 296) had ST deviation on the ECG and the MVO was related to the culprit lesion at coronary angiography; the 3rd had multi vessel PCI; and the 4th was not investigated further.

Table 5-24: Selected clinical characteristics of patients with a discharge diagnosis of acute and prior myocardial infarction

No.	Age, yrs	Sex	ECG	TnI	DE, g	LVEF (%)	Infarct loc. 1	Infarct loc. 2	Culprit vessel
34	76	F	Inf STE	19.2	64.4	53.11	Ant	Inf	-
89	75	M	Normal	8.4	15.9	43.05	Ant	Lateral	-
95	64	M	Lateral ST Dep	112	30.5	55.53	Ant	Lateral	3vd
104	51	M	Ant Q waves	7.9	32.3	39.3	Ant	Inf	LCx
110	73	F	Ant Q waves	6.2	7.7	80.14	Inf	-	-
117	53	M	Inf Q waves	1.6	5.1	58.12	Inf	-	2vd
149	50	M	Inf STE	34.4	21.4	53.12	Ant	Inf	LAD
201	65	M	Normal	9.7	8.4	69.75	Inf	Lateral	3vd
218	78	F	Ant Q waves	5.8	12.0	59.68	Ant	-	-
272	40	F	Inf STE	12.7	12.0	58.98	Ant	Lateral	3vd
296	58	M	Inf ST Dep	30.8	40.1	51.9	Ant	Inf	RCA

No., patient study number, M, male, F, female; DE, delayed hyperenhancement, loc., location, STE, ST elevation, Dep, depression, Ant., anterior, Inf, inferior, 2 or 3vd, 2 or 3 vessel disease at coronary angiography (>70% stenosis)

**Patient example 1: Acute and prior MI, patient number 149**

There is MVO associated with the inferior but the not anterior MI **Figure 6-13**. This is possibly due to difference in size and transmural, but acuteness may contribute. The admission ECG showed inferior ST elevation and thrombolysis was administered. At inpatient coronary angiography the culprit artery was a distal LAD occlusion with residual clot, no PCI was possible. It is possible that the culprit lesion was actually more proximal and there was embolisation into a diagonal branch (causing the basal anterior DE) and into the distal part of a “wrap-around” LAD (infero-apical DE).

**Patient example 2: Acute and prior MI, patient number 34**

A 76 year old female presented within 2 hours of chest pain and inferior ST elevation on ECG. She was thrombolysed and successfully reperfused by 90 minute ECG criteria resolution.

Coronary angiography was not performed. Routine echo contained no mention of LV aneurysm and concluded, “There is mild/ moderate LV dysfunction, infero-posterior segment thinned and hypokinetic. LV dilated distally.” At ceMRI there was a localised aneurysmal segment in the mid lateral wall with significant thinning **Figure 6-14**. LVEF was 53%, the patient did not return for follow up scans but she had not experienced a MACE at 3 years.

### Troponin I negative patients

Nine patients with a mean (SD) age of 64 (11) years, 6 (67%) of whom were male had evidence of prior myocardial infarction by ceMRI but negative TnI **Table 5-25**. Cardiovascular risk profile: current smoker (n=5); hypertension (n=4); hypercholesterolaemia (n=1); positive family history (n=4); and diabetes (n=1). The highest TIMI score was 4 (two patients).

Table 5-25: Selected clinical characteristics of patients with a final discharge diagnosis of prior (silent) myocardial infarction

No.	Age, yrs	Sex	ECG	CK, IU/ml	TIMI score	DE, g	Infarct loc.	LVEF (%)	Culprit vessel
69	60	M	Normal	191	1	3.2	Inf	54	3vd
115	81	M	LVH	113	3	5.6	Lateral	74	-
118	44	M	Ant STE	270	2	3.0	Lateral	72	-
124	67	F	LVH	65	3	0.9	Ant	71	-
147	74	M	Inf Q waves	132	4	8.2	Inf	50	-
221	70	F	Normal	65	3	6.7	Lateral	66	-
231	55	M	LBBB	84	3	7.6	Ant	12	Normal
240	58	M	Inf TWI	102	1	6.4	Inf	52	RCA
293	71	F	Inf ST dep	159	4	9.3	Inf	65	-

LBBB, left bundle branch block; TWI, T wave inversion; dep., depression.

Only one patient was correctly identified as “old infarction” by the ECG core lab (inferior Q waves). ECG core lab findings in the remainder: normal (n=2); LBBB (n=1); subendocardial

ischaemia (n=1); T wave inversion (n=1); LVH (n=2); and acute anterior MI (n=1).

Three patients had diagnostic coronary angiography with the following diagnoses and treatment: normal arteries (n=1); 3 vessel disease (n=1), referred for CABG; significant RCA disease (n=1), follow on PCI. Infarct size by ceMRI varied from 0.9 – 9.3g.

Infarct location was inferior or lateral in 7/9 (78%): inferior (n=4); lateral (n=3); and anterior (n=2). Three patients (33%) were discharged on secondary prevention therapy (aspirin, ACE inhibitor, beta blocker and statin). One patient was started on aspirin alone. LV ejection fraction was above 50% in six patients.

### ***Patient example 3: Prior myocardial infarction, patient number 221***

A 70 year old female smoker presented with chest pain described as a, “discomfort”. She had a past medical history of hypertension and a positive family history. TIMI risk score of 3, normal ECG, TnI negative and peak CK 65 IU/ml. CeMRI was performed 25 hours from onset of pain and showed DE in basal lateral segments and infarct size of 6.1 g (8% LV)

### **Figure 6-15.**

Infarct size was similar at 28 days (6.8g) and 6 months (6.8g). LVEF was 65% during admission and 67% at 6 months with no regional wall motion abnormality. The patient was discharged on aspirin alone and there was no MACE up to 3 years.

### ***Patient example 4: Prior myocardial infarction, patient 231***

A 55 year old male, with no standard cardiovascular risk factors presented with chest pain as primary symptom. He denied significant dyspnoea and was NYHA functional class 2. His alcohol consumption was >50 units per week. ECG showed LBBB with QRS duration 167ms

and a chest X ray showed cardiomegaly with clear lung fields. Cardiac catheterisation revealed smooth epicardial arteries, an LV end diastolic pressure of 4 mmHg and mean pulmonary artery wedge pressure of 7 mmHg. The official report of both the LV-gram and echo state that there is a possibility of LV thrombus. CeMRI was performed at 74 hours following onset of chest pain (**Figure 6-16**).

CeMRI revealed a dilated LV with severely impaired systolic function (LVEF 12%, LVEDV 442 ml, LVESV 389ml and LV mass 275g). Early MVO was seen at one minute (upper right) in a similar location to the thin rim of anterior subendocardial DE (lower right). Mean transmural score was 1.2 and endocardial extent 60°. No thrombus was seen. He was started on aspirin, ACE I, beta blocker, statin. Frusemide was reduced to 40mg because of low filling pressures and he was advised to abstain from alcohol altogether.

Follow up ceMRI scans were performed at 35, 176 and 361 days (**Figure 6-17**). LVEF and dimensions improved up to one year (LVEF 11, 19 and 32%; LVEDV 436, 392 and 200ml; LVESV 388, 317 and 136ml); most change occurred between six months and a year. There was also a change of cardiac axis between 6 month and 1 year scans. There was a minor change in LV mass over the same time period (LV mass 236, 210 and 204g).

### **Minimal myocyte necrosis**

Nine patients with a mean (SD) age 55 (9) years, 7 (78%) of whom were male had a positive TnI (median (IQR) 1.3 (0.7-2)) but no evidence of DE on ceMRI.



Table 5-26: Selected clinical characteristics in patients with a discharge diagnosis of minimal myocyte necrosis

No.	Age	Sex	ECG	TnI, ng/ml	CK, IU/ml	LVEF (%)	TIMI score	Culprit vessel
13	58	M	Normal	0.3	208	75.62	2	3vd
61	60	F	Normal	1.3	99	63.81	2	-
78	51	M	LVH	1.8	111	61.84	4	LCX
80	53	M	Inf Q waves	4.4	841	74.56	4	minimal
83	46	M	Normal	0.5	172	73.32	2	LCX
97	63	M	LVH	2.3	749	37.39	4	2vd
109	40	F	Normal	0.7	121	68.04	3	RCA
193	67	M	Inf ST dep.	2	111	66.8	5	RCA
211	60	M	Normal	0.9	168	53.8	2	-

LVH, left ventricular hypertrophy, minimal, indicates <25% stenosis (for this patient in the RCA). Remainder of abbreviations as in previous tables.

The median (IQR) peak creatine kinase value was 168 (111-208) IU/l. The highest TnI value was 4.4ng/ml and in this patient the diagnosis of Takotsubo cardiomyopathy was made by ceMRI. The next TnI value was just under half that (2.3 ng/ml). The diagnoses by ECG were: normal (n=5); LVH (n=3); and subendocardial ischaemia (n=1). TIMI risk score ranged from low/ moderate to high risk in 1 patient. LVEF was normal in the majority of patients (mean (SD), 64 (12) %). Diagnostic coronary angiography was performed in seven and significant disease was seen in six. Five were suitable for inpatient PCI and the sixth underwent CABG.

**Patient example 5: Minimal myocyte necrosis, patient number 80**

A 53 year old male was admitted with 90 minutes of significant chest pain and ECG showed widespread deep T wave inversion with borderline anterior ST elevation **Figure 5-11**. The QTc was elevated at 474ms.



**Figure 5-11: Presenting ECG in patient with final discharge diagnosis of Takotsubo cardiomyopathy**

Due to a recent history of upper gastrointestinal bleeding it was decided to perform emergency cardiac catheterisation with a view to primary angioplasty. At angiography there was plaque disease at most in the mid LAD. An LV gram was performed and reported as showing, “hypokinetic apical segments of the anterior wall”. Subsequent troponin was elevated at 4.4 and CK 841. Risk factors included smoking, positive family history for premature cardiovascular disease and treated hypertension. The TIMI score was 4. CeMRI was performed 25 hours after the onset of chest pain. On the SSFP images there is obvious apical ballooning, best seen in the LV outflow tract views (**Figure 6-18**). Upper panels, left shows end diastole and right shows end systole.

The corresponding DE imaging was negative and LV ejection fraction was 75%, LV mass elevated at 175 g, LVEDV (120 ml) and LVESV (27ml) were within normal limits. The patient returned for follow up scan 58 days later. LV dimensions were similar (LVEF 80%, LV mass

173g, LVEDV 104ml and LVESV 21ml). The apical ballooning had resolved leaving no regional wall motion abnormality and again there was no evidence of DE.

The diagnosis is in keeping with Takotsubo cardiomyopathy and shows that there was no irreversible damage and that the regional wall motion abnormality had resolved by 2 months. The TnI level (4.4ng/l) is the highest value at which DE was not detected and is almost twice the next value in this series of patients (2.3ng/l).

### Prior non-ischaemic fibrosis

Five patients with a mean (SD) age of 54.8 (12.7) years 4 of whom (80%) were male presented with chest pain, normal TnI and subendocardial sparing pattern of DE **Table 5-27**.

Table 5-27: Selected clinical characteristics of patients with a discharge diagnosis of prior non-ischaemic fibrosis

No.	Age, yrs	Sex	ECG	CK, IU/l	Creat., mmol/l	DE, g	DE loc.	LVEF, %	LVM, g
29	54	F	Inf Q waves	82	112	13.1	Lateral	78.28	109.28
77	35	M	Normal	137	95	1.2	Lat	52.59	122.41
112	55	M	Normal	150	94	1.5	Lat	65.26	150.02
230	60	M	Normal	449	81	24.5	Lat	82.87	245.37
255	70	M	Pericarditis	103	104	5.6	Lat	67.4	141.27

Creat., creatinine; LVM, left ventricular mass

The ECG was normal in three, showed features of an old inferior MI in one and widespread saddle shaped ST elevation with a CRP of 142 in keeping with pericarditis in another. All

patients were low risk by TIMI scoring. Coronary angiography was performed in one patient and showed no significant disease.

All had subendocardial sparing on ceMRI and all were in the basal lateral location (**Figure 6-19**). It was possible to planimeter the regions of DE and the size varied from 1.2 to 24.5 g.

LVEF was over 50% in all cases and there were no regional wall motion abnormalities. The LV mass was normal in four patients and markedly elevated in the fifth (see example below). The aetiology of hyperenhancement in the four patients with normal LV mass is not clear.

There are a number other conditions described that have been associated with DE (myocarditis (21), sarcoidosis (28), amyloidosis (29), dilated cardiomyopathy (30), hypertrophic cardiomyopathy (31) and chronic renal failure (32)). None of these patients had a history in keeping with these diagnoses and renal function was normal.

#### ***Patient example 6: Prior non-ischaemic fibrosis, patient 230***

A 60 year old male with a past history of treated hypertension and type II diabetes presented with ischaemic chest pain. Admission ECG was normal. CeMRI demonstrated marked left ventricular hypertrophy (LV mass 245 g) and LV systolic function was hyperdynamic (LVEF 83%). LVEDV was elevated at 180ml and the LVESV was low at 30ml (**Figure 6-20**). There is patchy DE that is localised to the basal lateral segment (upper panels). There is concentric LVH and with LV cavity obliteration in systole (lower right). At TTE the gradient across the aortic valve was 13 mmHg and the aortic valve was not calcified. NtBNP was 319 during admission and 191 at 6 months.

Unstable angina

Eleven patients with a mean (SD) age of 56(14) years, 4 (36%) of whom were male presented with chest pain, were TnI negative and had no evidence DE on ceMRI **Table 5-28**. The additional qualifying factors for unstable angina included either significant ST segment depression or significant coronary disease at inpatient angiography or positive exercise tolerance test (Full Bruce Protocol).

Table 5-28: Selected clinical characteristics of patients with a discharge diagnosis of unstable angina

No.	Age, yrs	Sex	ECG	CK, IU/ml	TIMI score	NtBNP, ng/l	LVEF, (%)	Culprit vessel
52	47	F	Normal	91	1	10.9	71.29	Minimal
101	52	F	Normal	45	1	371	62.51	RCA
125	46	F	Normal	204	1	238	63.94	LAD
126	48	M	SEI	126	2	18	59.8	RCA
139	56	M	Ant Q waves	153	2	89.5	75.55	-
166	34	M	Normal	59	1	48.8	64.01	LCX
204	55	F	Normal	67	2	158	78	-
237	69	F	SEI	84	3	175	61.44	-
249	49	M	LBBB	112	1	187	44.38	-
256	82	F	Normal	96	2	769	80.62	2vd
261	77	F	Normal	30	2	141	75.99	RCA

SEI, subendocardial ischaemia

ECG diagnosis: Normal (n=7); LBBB (n=1); old anterior (n=1); subendocardial ischaemia (n=2). All patients, except one (TIMI score =3), had a low risk TIMI score. Seven underwent coronary angiography: one patient had minimal disease but severe coronary spasm; one patient had multi vessel disease and the remaining five had single vessel disease; LAD (one), LCx (one) and RCA (three). All patients were suitable for follow on angioplasty and stenting. One patient

(patient number 204) had a normal presentation ECG but went on to have a positive exercise test. Coronary angiography was not performed and she was treated medically.

Chest pain, other

Forty eight patients with a mean (SD) age of 51 (11) years 30 (63%) of whom were male were admitted with chest pain and subsequently had a negative TnI and no DE. The discharge diagnosis was taken from the patients discharge letter and was determined by the Consultant Physician (Cardiology or General Internal Medicine) Table 5-29.

Table 5-29: Selected clinical features of patients in the “chest pain, other” diagnostic group by a more specific discharge diagnosis if available

	N	Sex, M	Age, yrs	Risk factors				Presenting ECG				ceMRI LVEF, %	TIMI score
				Smoker	FH	BP	Chol.	Normal	LVH	LBBB	ST dev.		
<i>Diagnosis</i>													
Chest pain, ?cause	30	16 (53)	53.4 (10.7)	18 (60)	15 (50)	13 (43)	10 (33)	26 (87)	3 (10)	1 (3)	0 (0)	66.4 (8.3)	1 (1.5-2)
Musculoskeletal	7	5 (71)	47.8 (17.1)	5 (71)	5 (71)	1 (14)	0 (0)	4 (57)	2 (28)	0 (0)	1 (14)	62.2 (5.9)	2 (1.5-2)
GORD	7	6 (86)	44.8 (5.3)	7 (100)	5 (71)	2 (28)	1 (14)	7 (100)	0 (0)	0 (0)	0 (0)	67.3 (8.3)	1 (1-1)
Pericarditis	2	2	45 and 59	0	0	0	0	1	1	0	0	66.8 and 59.2	1 and 1
PAF	1	1	43	1	0	0	0	0	0	0	1	64.8	2
LRTI	1	0	44	1	1	0	0	1	0	0	0	71	1

All available data used, n is the maximum number of patients in each group. Data are presented as mean (SD) for continuous variables (median (IQR) for TIMI score) and number (%) for categorical variables. When the number of patients in a diagnostic group < 7 individual cases are presented. FH, family history cardiovascular disease; BP, treated hypertension; Chol, treated hypercholesterolaemia; LVH, left ventricular hypertrophy; LBBB, left bundle branch block; ST dev., ST segment deviation; LVEF, left ventricular ejection fraction; TIMI, Thrombolysis In Myocardial Infarction risk score (0-7); GORD, gastro-oesophageal reflux disease; PAF, paroxysmal atrial fibrillation; LRTI, lower respiratory tract infection.

All patients had a low TIMI risk score with normal LV systolic function. The ECG characteristics were: normal (n=45), LVH (n=2), LBBB (n=1). Thirty (62.5%) patients received the label “chest pain, unknown cause”, indicating all basic investigations were normal. Seven out of forty eight (15%) patients had a diagnosis of musculoskeletal chest pain and 7/48

(15%) were labeled Gastro-oesophageal Reflux Disease based on the nature of chest pain and upper GI endoscopy if performed.

The diagnosis of pericarditis was made in 2 patients based on history alone. A further patient had atrial fibrillation and rate related ST depression on the presenting ECG. She reverted to sinus rhythm spontaneously and subsequent coronary angiography was normal. One patient developed consolidation on her chest X-ray so discharge diagnosis was of bronchopneumonia. Out of the 48 patients, two patients had reached an end point of MACE/ death at 3 years. One patient underwent elective percutaneous intervention and the other was dead (murdered).

One of the patients with LVH met the ST elevation criteria and was thrombolysed inappropriately and there were no evolving electrocardiographic changes. The patient with LBBB went on to have a normal coronary angiogram. On further inspection of the 48 ceMRI scans, 47 were entirely normal. One patient (number 164) had a dilated aortic measuring 41 mm at the sino-tubular junction in the LVOT view root (**Figure 6-21**). This patient attended for all four follow up visits and there was no change in the dimensions over this time. A central jet of mild aortic regurgitation is seen as a flow void. None of these patients had evidence for ischaemic heart disease.

### **Right ventricular infarction**

Twelve patients with a mean (SD) age 59 (14) years and 10 (83%) of whom were male had evidence of RV infarction by ceMRI **Figure 6-22**. These 12 patients comprised 15% of all TnI positive patients and 11/33 (33%) of all inferior infarcts. In only 2 patients (17%) was RV involvement suspected at transthoracic echocardiography. The mean (SD) RV infarct size was 25.6 (20.5) g on admission and by visit 2 had fallen to 12.1 (14.3) g, a reduction of 53%. The

mean (SD) RV infarct size comprised 40 (17) % of the total (RV + LV) infarct burden. By presenting ECG, 5 had ST elevation, 4 had ST depression and 3 were normal. Eight patients received thrombolysis.

### **LV thrombus**

Five patients with a mean (SD) age of 65 (10) year and 4 (80%) of whom were male had evidence of LV thrombus by ceMRI, which comprises just over 6% of all troponin positive patients **Figure 6-23**. All had TTE and in no patients was LV thrombus detected. All were started on warfarin following the results of ceMRI and thrombus was not visible in any scans at 6 months. Four presented with anterior ST elevation and were thrombolysed. The fifth presented with significant ST depression. By ceMRI the infarct location was anterior in 4 and anterior plus inferior (acute and prior infarctions) in the fifth, all involved basal segments.

LV thrombus therefore complicated 4/21 (19%) of anterior myocardial infarctions in this population. The mean (SD) infarct size was 68 (34) g or 47 (26) % of LV mass and TnI was 155 (169). By visit 2 the infarct size had fallen to 46 (18) g a mean reduction of 32%. Three patients had late MVO and 4 had the maximum mean transmural score of 4. The fifth patient had a smaller infarction of 32g that was neither transmural nor had MVO. There was a localised aneurysmal segment in the apex that contained thrombus. The mean (SD) LVEF was 39 (8) % on admission rising to 42 (11) % at 6 months. A proximal occlusion was confirmed at coronary angiography in 3 patients. In 2, the culprit vessel was the proximal LAD and in the third it was the LCx.



# 6 Illustrations - ceMRI

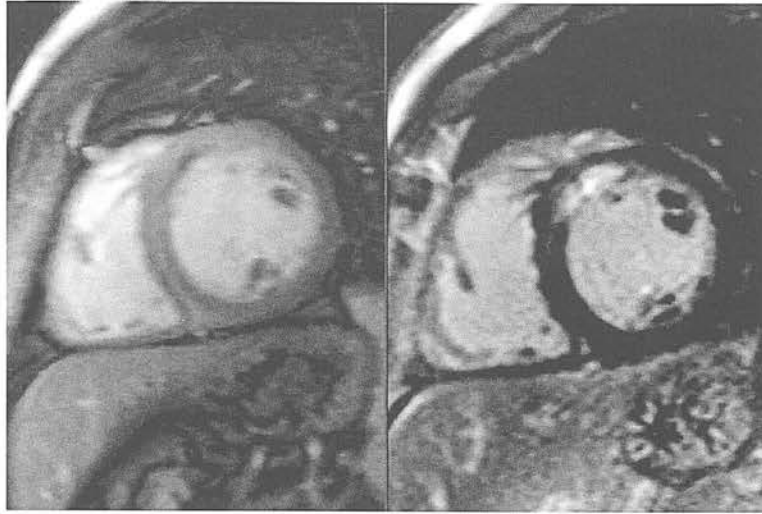


Figure 6-1: CeMRI mid left ventricular SA slices showing early MVO (left) and corresponding DE image with no late MVO (right)

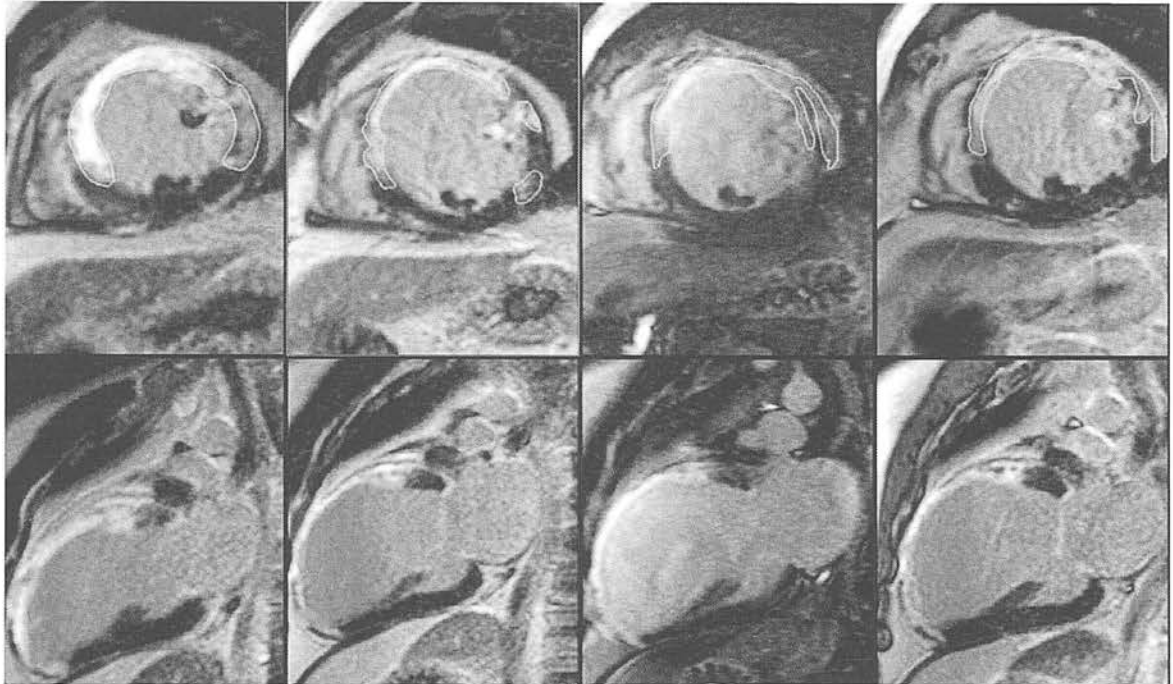


Figure 6-2: Series of DE images illustrating DE area planimetry in the same patient at 2, 38, 260 and 380 days post AMI (left to right)

Upper panels, SA view. Lower panels, 2 chamber view

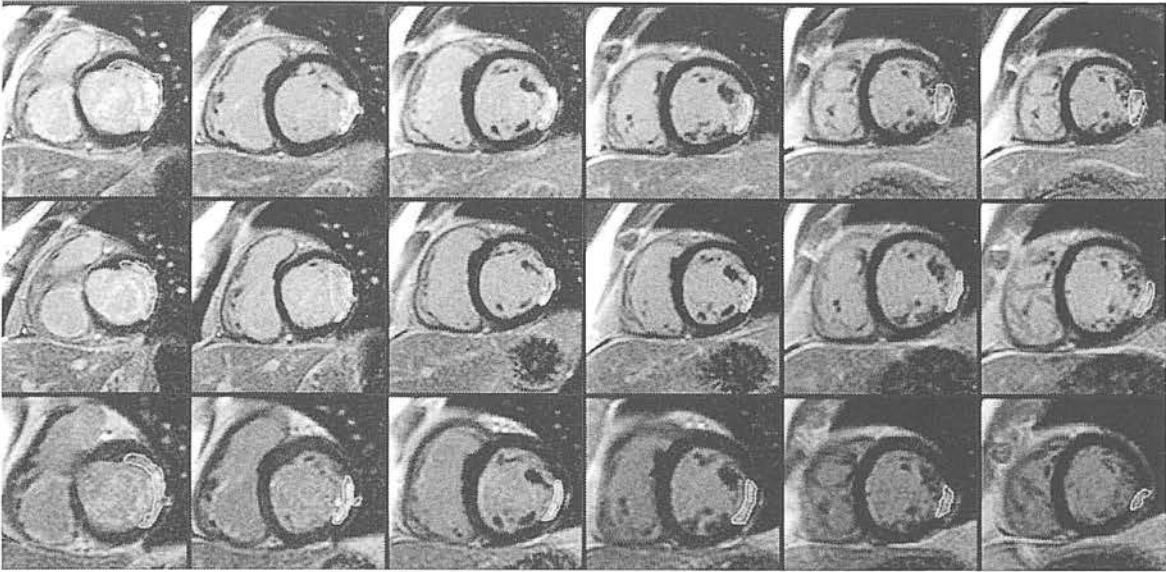


Figure 6-3: SA stacks showing infarct planimetry in the same patient from base to apex (left to right) for 3 separate visits

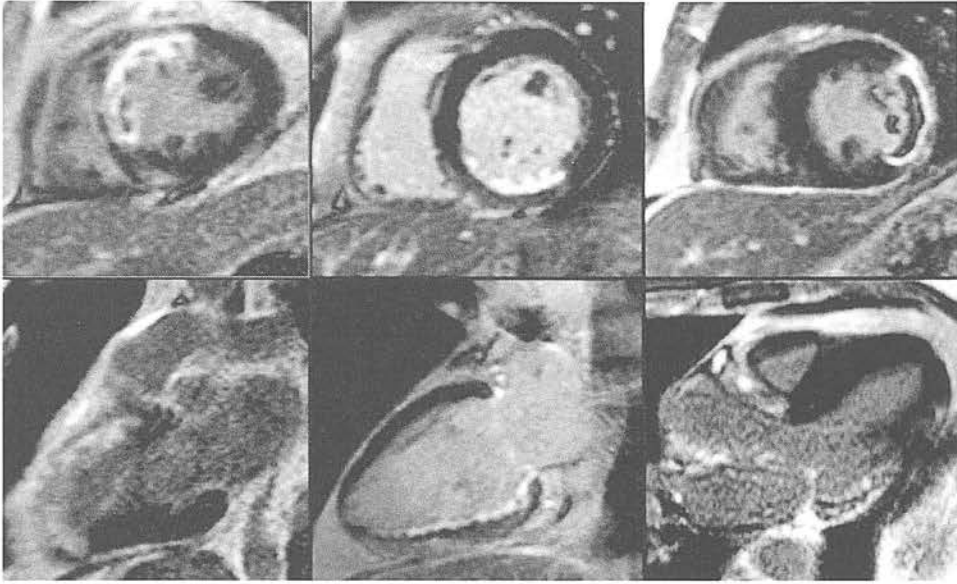


Figure 6-4: Short and long axis images of the three infarct locations  
Left - anterior; middle - inferior; and right - lateral

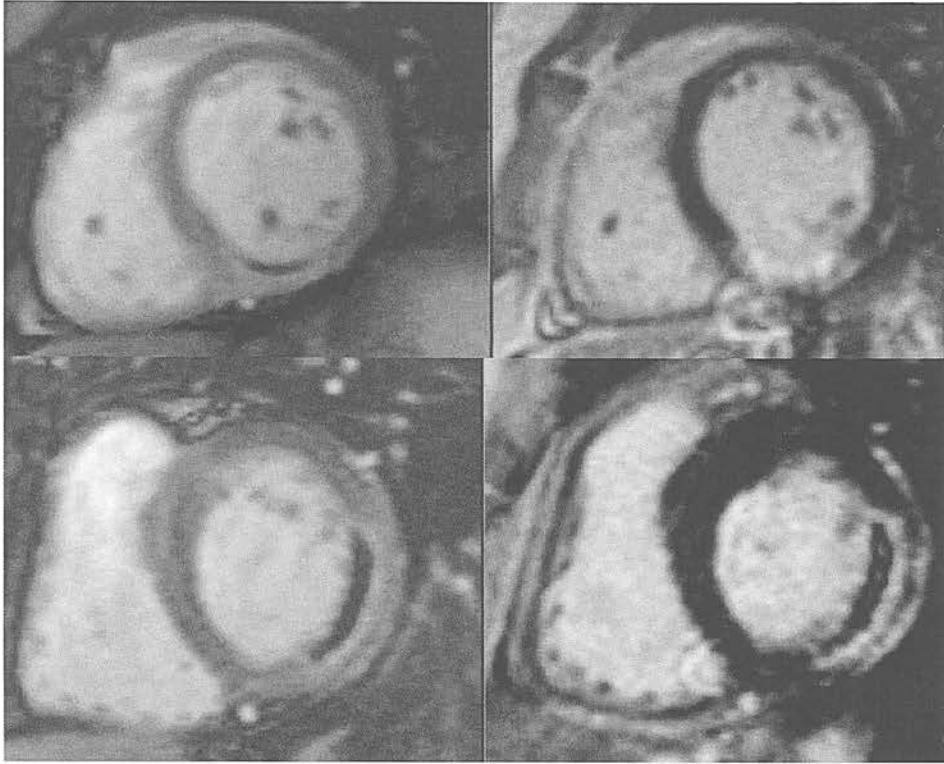


Figure 6-5: SA scans showing 2 patterns of MVO in 2 patients  
Early MVO only (upper) and early plus late MVO (lower)

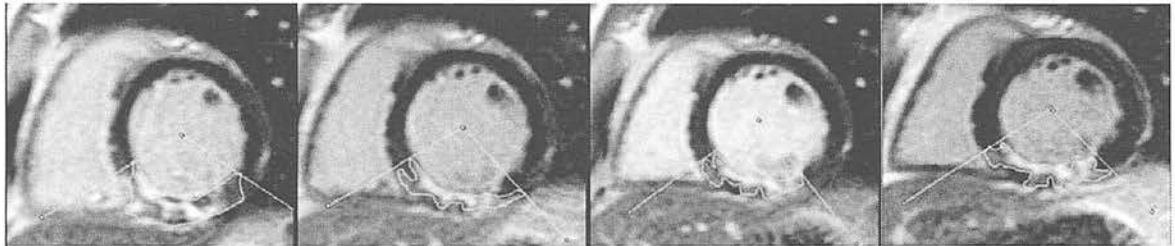


Figure 6-6: Series of mid ventricular SA images from admission to 1 year in the same patient illustrating infarct planimetry and calculation of endocardial extent.

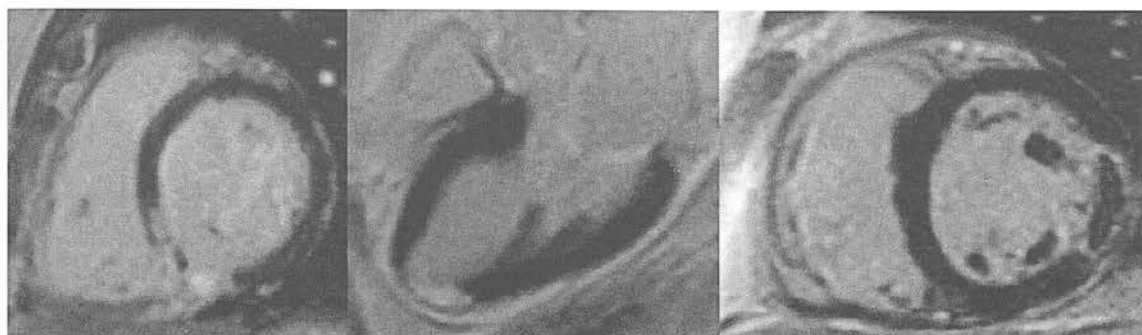


Figure 6-7: DE in three patients with positive TnI but normal coronary arteries

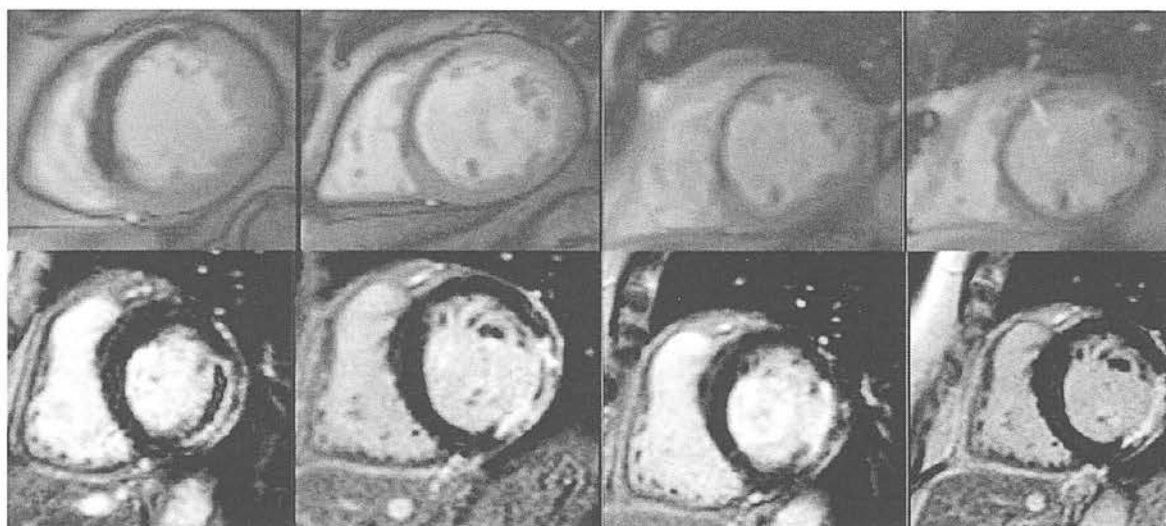


Figure 6-8: Persistence of early MVO in the anterior region out to 1 year (upper)  
Persistence of late MVO in the lateral region out to 28 days, resolving by 6 months (lower)

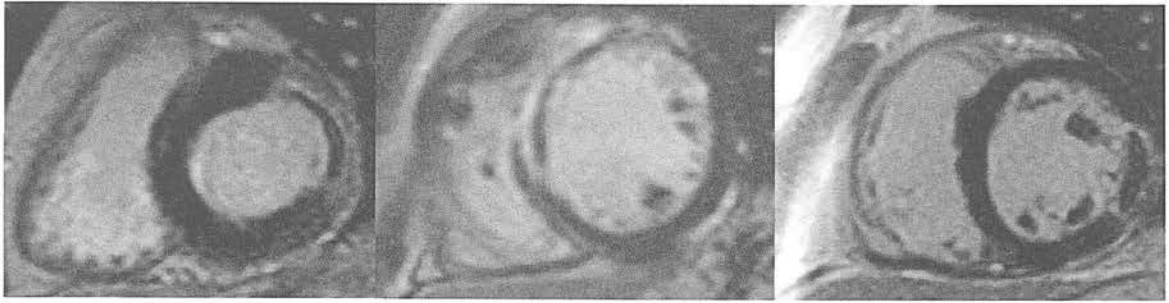


Figure 6-9: Three patients with late MVO and CRP < 26 mg/L

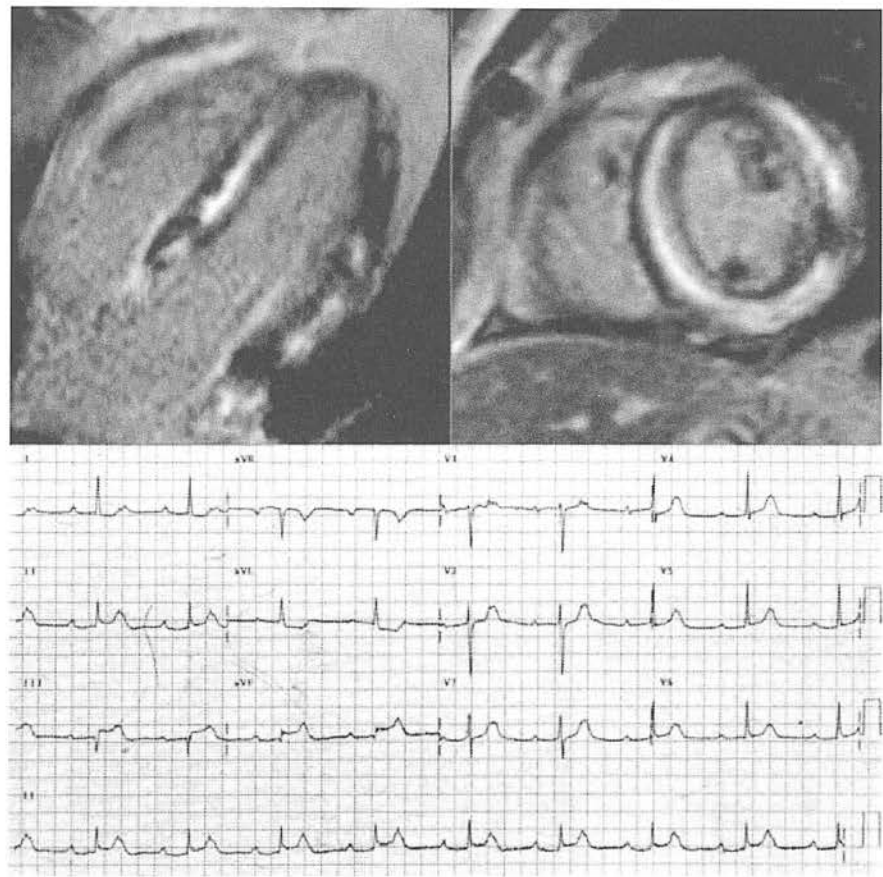


Figure 6-10: Acute myocarditis  
 4 chamber (left) and SA (right) DE images during admission showing subendocardial sparing (upper)  
 Presenting 12-lead ECG showing acute inferior ST elevation (lower)

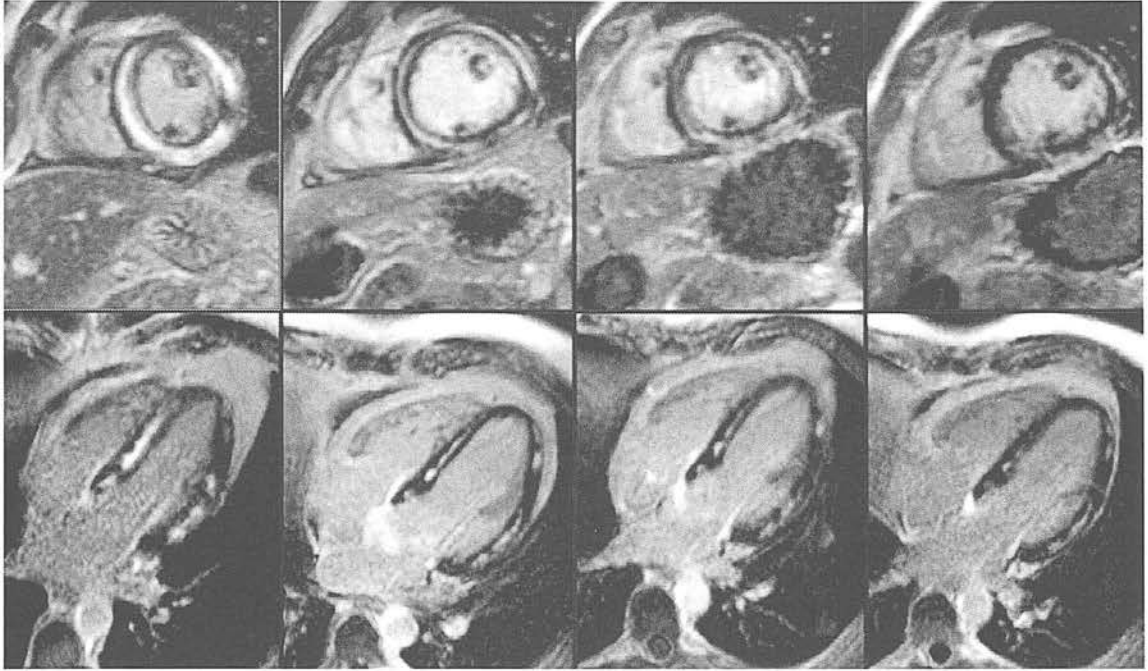


Figure 6-11: Evolution of acute myocarditis by ceMRI at 3, 31, 155 and 368 days  
SA (upper) and 4 chamber (lower)



Figure 6-12: Two chamber view of multiple infarcts by ceMRI  
Small anterior (mid ventricle) and larger inferior (mid ventricle)





Figure 6-13: Multiple infarcts by ceMRI  
 SA views showing small basal anterior (left) and larger apical inferior (centre)  
 2 chamber view showing both infarcts (right)

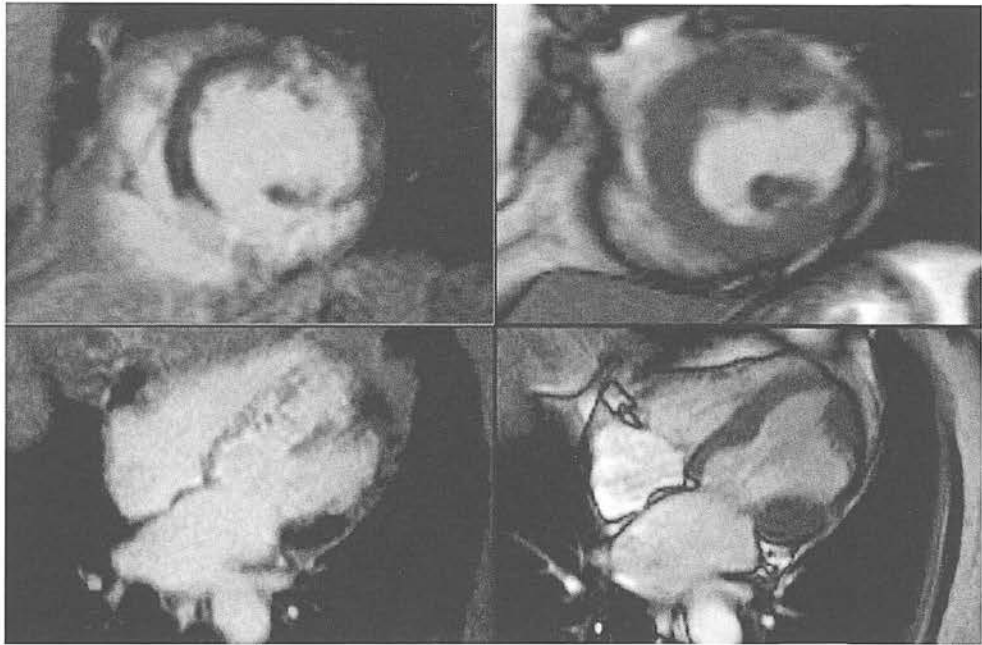


Figure 6-14: Multiple infarcts by ceMRI  
 SA and 4 chamber DE (left) showing septal and lateral infarcts  
 Corresponding SA and 4 chamber SSFP end diastolic stills (right) showing a  
 localised thinned and aneurysmal segment of the mid lateral wall

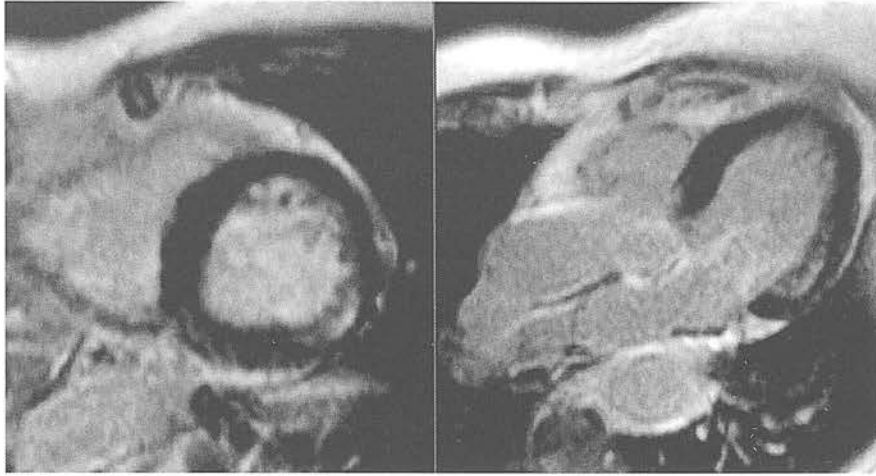


Figure 6-15: Prior (silent) MI by ceMRI showing DE in the basal lateral segments SA (left) and LV outflow tract (right)

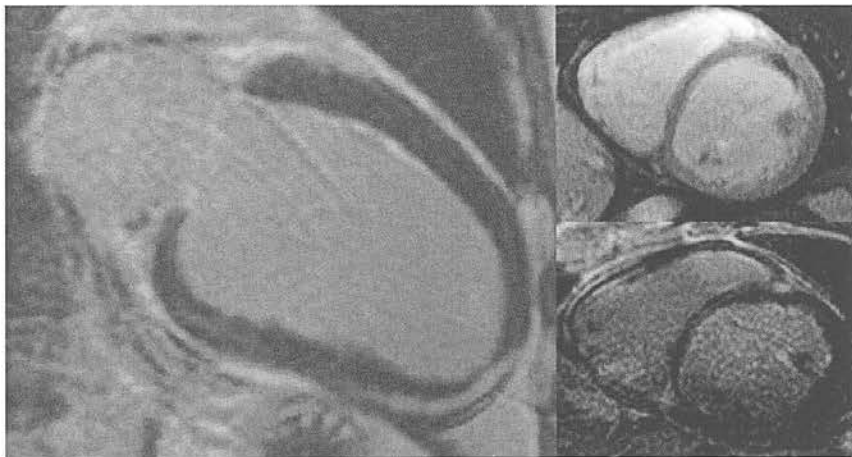


Figure 6-16: Prior (silent) MI by ceMRI showing a thin strip of subendocardial DE in the basal and mid anterior segments

2 chamber DE image (left)

SA views post Gd-DTPA at identical slice positions (right) showing early MVO only at 1 o'clock (upper)

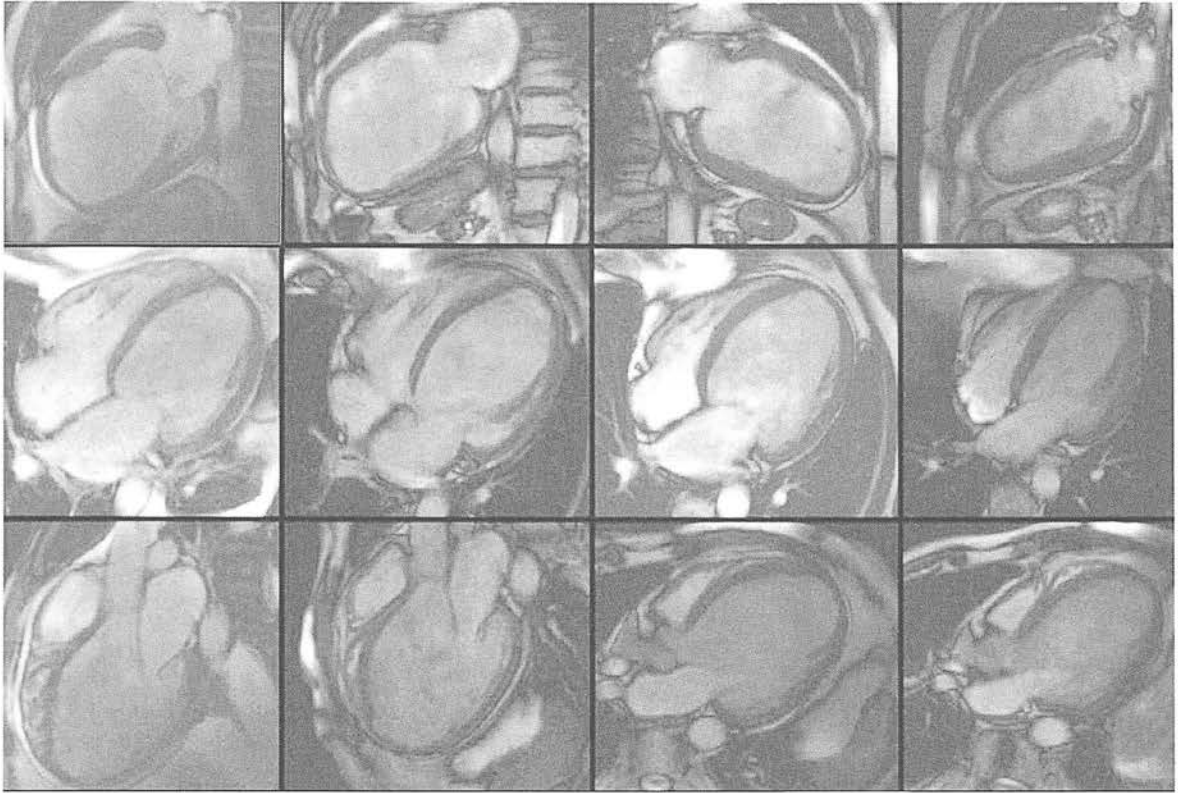


Figure 6-17: SSFP images showing reduction in LV dimensions with medical therapy in a patient with DCM at 3, 35, 176 and 361 days (left to right)

2 chamber (upper), 4 chamber (middle) and LV outflow tract (lower)

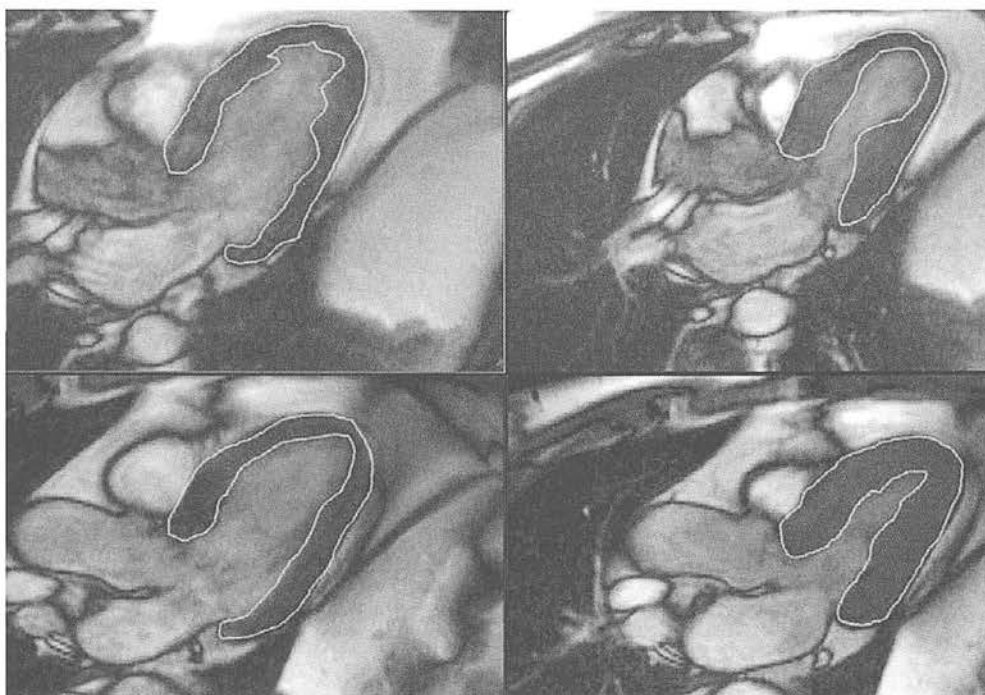


Figure 6-18: Takotsubo cardiomyopathy by ceMRI at 1 day (upper) and 58 days (lower) showing resolution of apical ballooning

SSFP LV outflow tract views at end diastole (left) and end systole (right)

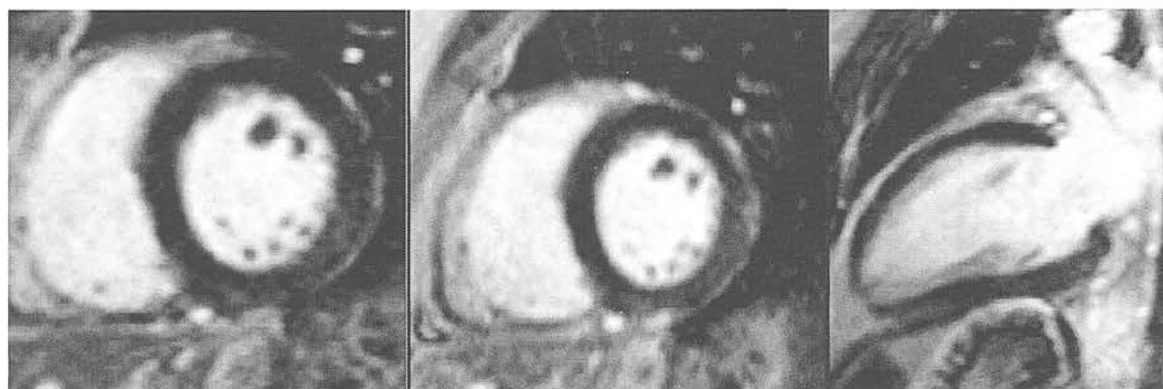


Figure 6-19: Prior non-ischaemic fibrosis by ceMRI

There is inferolateral subendocardial sparing of DE at 5 o'clock in 2 contiguous SA slices (left and middle) that is confirmed in the 2-chamber view (right)

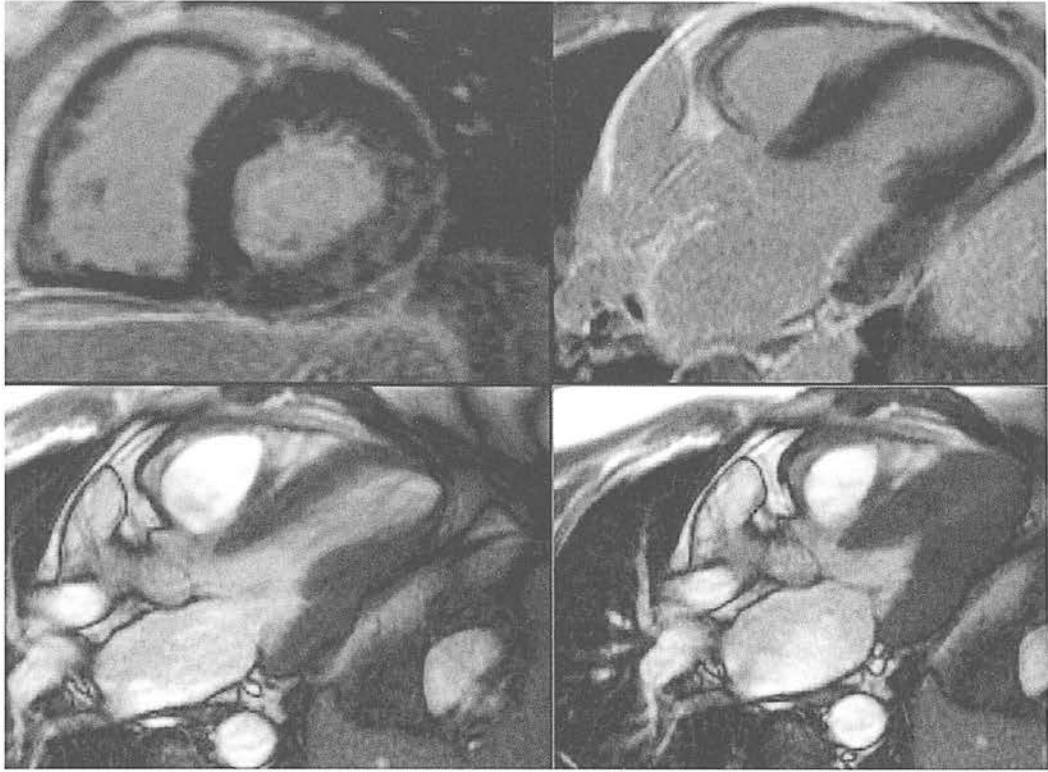


Figure 6-20: Prior non-ischaemic fibrosis by ceMRI

DE images (upper), SA view shows subendocardial sparing of DE at 5 o'clock (left) that is confirmed in the LV outflow tract view (right)

SSFP images (lower) of the LV outflow tract in end diastole (left) and end systole (right) showing mid- and apical ventricular cavity obliteration

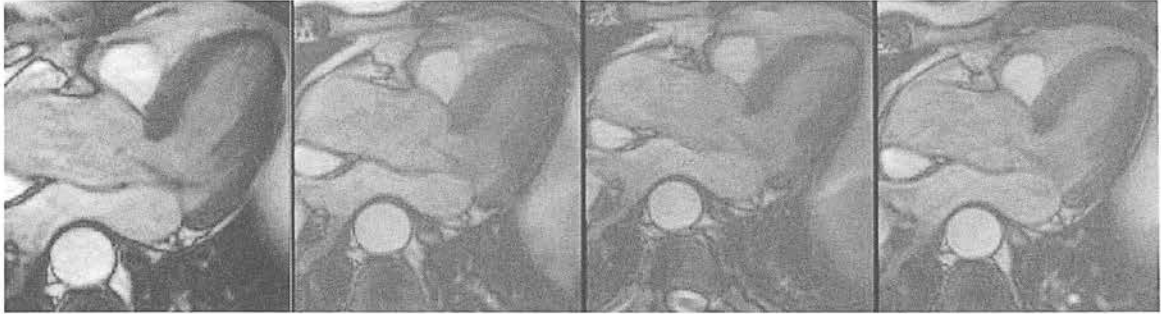


Figure 6-21: Dilated aortic root and mild aortic regurgitation by ceMRI at 5, 31, 185 and 366 days following admission with chest pain (left to right)  
 SSFP LV outflow tract images at end diastole showing a dilated aortic root and a flow void at the aortic valve indicating aortic regurgitation

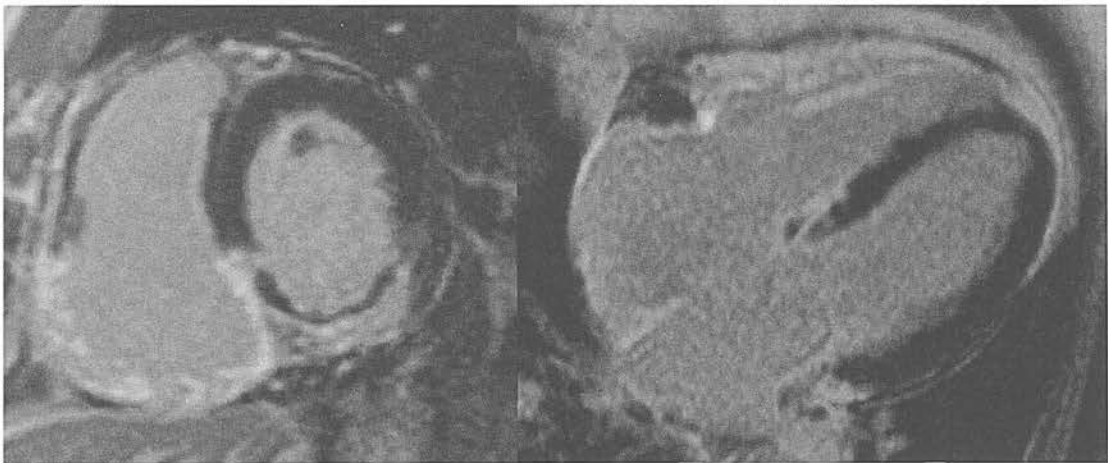


Figure 6-22: Acute right ventricular myocardial infarction by ceMRI  
 SA (left) and 4 chamber (right) views showing DE in the inferior LV wall (with late MVO) that extends into the RV

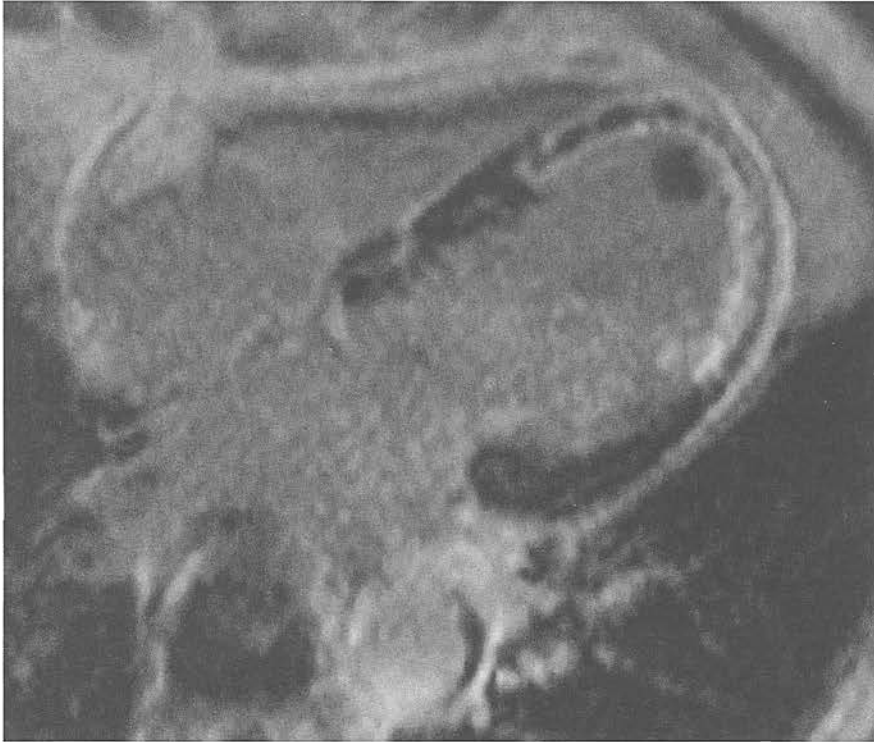


Figure 6-23: Apical LV thrombus in AMI by ceMRI

DE 4 chamber view showing an extensive anterior mid and apical transmural MI with late MVO and apical LV thrombus



## 7 Discussion

CeMRI is superior to any other available noninvasive imaging technique for identification, localisation and quantification of myocardial infarction in both its acutely necrotic and chronically fibrotic states (31;33;109;170). In addition, it is possible to discern certain characteristics of the myocardial scar such as microvascular obstruction.

Over a 9 month period between August 2002 and May 2003, all patients admitted to the Western Infirmary, Glasgow with their first presentation of chest pain to rule out myocardial infarction were considered for this study. The final study population consisted of 153 consecutive patients that did not meet any of the exclusion criteria. This represents 12 % of the total population that underwent an “MI screen” and 54% of those presenting for the first time. Patients were included on the basis of history and collaboration with case records to confirm initial presentation. The reasons for exclusion fell into 6 broad categories: past medical history; comorbidity; consent; contraindications to ceMRI; geography and other. The most frequent contraindication was a past medical history of chest pain or confirmed ischaemic heart disease comprising 65% of the screened population.

The aim of this thesis was to study the role of ceMRI in two important diagnostic areas of the chest pain syndrome; the correct identification and then accurate quantification of myocardial infarction.

Early correct identification of myocardial infarction was investigated using ceMRI to determine the sensitivity and specificity of first ST elevation, then ST deviation on the presenting ECG.

Improved final diagnosis was investigated by performing ceMRI in broad population of



patients and the additional findings in patients with first historical hospital admission with an acute chest pain syndrome are presented.

To investigate the routinely available biochemical (8-12 hour TnI level) and bioelectrical (ECG at discharge, by Selvester score) means of estimating (reperfused and non-reperfused) infarct sizes, correlations with planimetered regions of subendocardial DE were made both individually and in combination with planimetered regions of subendocardial DE. For the measurement of infarct size it became apparent that it would be necessary to confirm that there was indeed a single acute MI using a combination of ceMRI, ECG and TnI. The 57 patients with “single AMI” comprised the largest diagnostic group seen in **Figure 5-4**. These patients had larger infarct sizes, reduced LV systolic function, increased LV dimensions and were at moderate risk by mean TIMI score. They were more likely to have diagnostic coronary angiography and  $\geq 1$  significant stenosis and there was a longer time to first ceMRI scan. The ceMRI findings in patients that were TnI positive but had a normal coronary angiogram are also described. The remaining patients are referred to as “non-single AMI” and described in section on additional findings by ceMRI.

Using measurements at 4 planned time points (admission, 28 days, 6 months and 1 year) the natural history of infarct size and characteristics was documented and reasons for different rates of change explored. These time points were also chosen to investigate LV remodelling and the hypothesis was that the genotype of the MMP-1 promoter sequence would have an influence. Finally, as part of investigations into the ACS, the role of inflammation was investigated by demonstrating both the correlation of CRP with infarct size and its ability to predict infarct characteristics.

## **7.1 ST segment deviation analysis of the admission 12-lead ECG as an aid to early diagnosis of AMI**

The biochemical methods for detection of AMI have become so sensitive that it is necessary to develop clinically relevant subgroups. The 1999 ESC/ACC consensus conference produced such a broad definition, on the basis of historical information and biochemical marker data, that any ECG criteria were rendered superfluous for making the final diagnosis (171). The current availability of aggressive emergency therapies for establishing myocardial reperfusion requires a method for establishing a rapid working diagnosis of thrombotic AMI at the time of initial pre-hospital or emergency department presentation. The performance of such a method can be determined by observing outcomes that range from aborted infarction to hemorrhagic complications due to inappropriate therapy(33;48;161). An immediately available clinical test with high sensitivity and specificity for thrombotic AMI is required, and neither the history nor the biochemical markers achieve this goal at present. ST-segment elevation has such high specificity for AMI that the currently accepted name of this patient subgroup is “ST-segment elevation MI,” conveniently termed “STEMI.” Indeed, the multiple randomised clinical trials in patients with ACS have either STEMI or Non-STEMI inclusion criteria.

This study highlights that, in patients with acute chest pain, ST-segment depression is often indicative of AMI, but does not aim to make any recommendations about treatment strategies.

Use of this method to confirm the high specificity and to determine the sensitivity of the existing ECG criteria requires the study of the broad population of consecutive patients admitted to a single medical centre with symptoms compatible with ACS. The present study was designed and implemented for this purpose.

Thirty-five (23%) out of 153 patients were excluded on the basis of ECG confounding factors. The removal of confounders, so often characterised by the early repolarisation that mimics the ST-segment deviation of acute transmural ischemia led to, for example, a surprising infarction rate by ceMRI of 29 of the 31 patients (94%) meeting the ACC/ESC ST segment elevation threshold(60). When considering the total population without exclusions, infarct by ceMRI was present in 32 of the 40 (80%) patients meeting the ST-segment elevation threshold. In addition, the sensitivity rose from 44% in the ACC/ESC STEMI group to 71% in the STEMI equivalent group with a reduction in specificity from 91% to 86%. As expected, these values demonstrate a reduced diagnostic accuracy both overall and between groups, but interestingly there is very little difference in the positive predictive values (83% vs. 82%).

The prevalence of infarction in this study population was high at 50% meaning positive predictive values for ACC/ECC STEMI and STEMI-equivalent criteria were 94% and 92%. Considering the lower AMI prevalence of 20% that is more typical of the population presenting to the Accident and Emergency; the PPV falls to 85% and 75% respectively. This extrapolation requires further investigation, if the results are to be applied more widely.

Eight patients were considered to have had multiple infarcts, 3 of whom had 3-vessel disease (one with critical left main stem stenosis); one had proximal and distal lesions in a dominant RCA; one had distal left anterior descending disease; one had normal coronaries; and for the final 2 patients coronary angiography was not clinically indicated. The distribution of STEMI/NSTEMI was equal, and all had a rise and fall in cardiac enzymes in keeping with AMI. It is possible that the patients with 3-vessel disease had multiple “hot plaques,” but it is more likely that there were chronic infarcts. Because there were no well-validated ceMRI

sequences for differentiating age of infarct at the time of recruitment, absence of either historical or ECG suggestion of infarct was required for study inclusion together with a rise and fall of troponin and/or CK-MB.

Consideration of presenting STEMI or STEMI equivalent criteria as “falsely positive” would be in error when the prompt administration of reperfusion therapy sufficiently aborts the AMI so that it is not detected by ceMRI. Fourteen patients presented to hospital within 1 h; 8 had an AMI by both ECG and ceMRI. None of the remaining 6 had significant ST-segment deviation, and the largest initial CK value was 134. Aborted AMI is therefore unlikely to be a significant confounder in this study.

There were no patients with a troponin I > 4.4 ng/ml who did not have DE, and the mean TnI for these 8 patients was 1.44 **Table 5-4**. This might indicate the upper limit of troponin that suggests a “necrosette,” and further studies on the significance of this change range using ceMRI in this lower-risk group might help in future risk stratification (172).

The similarity in infarct size by ceMRI between the STEMI and STEMI-equivalent groups highlights that significant infarcts are being missed by the ECG criteria used in typical clinical practice. It should be noted, however, that the naturally occurring AMI sizes of many of the 31 of 58 in the ceMRI-positive group who received reperfusion therapy would have been higher. This is further illustrated by the significantly lower time to presentation in the STEMI group (difference in median 3.3 hours), suggesting that this group had more severe symptoms. Myocardial infarcts that are missed altogether by the ECG are smaller, although the difference does not reach statistical significance ( $p = 0.29$ , Kruskal-Wallis test) **Figure 5-5**.

The additional diagnostic information provided by the STEMI-equivalent criteria resulted in increased detection in the anterior location from 38% (5 of 13) to 69% (9 of 13), in the inferior location from 70% (14 of 20) to 95% (19 of 20), in the posterolateral location from 36% (4 of 11) to 82% (9 of 11), and in the inferior and posterolateral location from 17% (1 of 6) to 67% (4 of 6).

In the present study, when maximal ST-segment deviation appeared as depression in V1, V2, or V3, 7 of the 9 patients had ceMRI-determined infarction in the posterolateral region of the LV; the remaining 2 did not but had 3-vessel disease. This maximal ST-segment deviation direction was falsely positive for infarction in none of the individuals. The basal region of the LV is superiorly oriented in the thorax, directly opposite the inferior or diaphragmatic region. When ST-segment depression in “inferior leads” accompanies ST-segment elevation maximal in V2 to V4, extension of the anterior infarction into the basal region has been documented, due to occlusion of the proximal LAD(173). In the present study, when maximal ST-segment deviation appeared as depression in II, III, and aVF, 4 of the 5 patients had ceMRI-documented infarction in the basal region of the LV. This maximal ST-segment deviation direction was only falsely positive in 1 individual with a body mass index of 33 who subsequently had a normal coronary angiogram. The term “ST-segment deviation MI” could be adapted with designation of the direction of the lead with the maximum either ST-segment elevation or ST-segment depression. The negative leads are as “real” as the positive leads, and indeed lead “-aVR” replaced +aVR in Sweden 30 years ago(174). With either alternative, the identification of the spatial direction of the ST-segment as indicated by the lead with the maximal deviation would be required. This study has documented that in patients admitted to

hospital with chest pain and no historical or ECG evidence for previous AMI only 50% of the AMI group are identified by the ACC/ESC STEMI criteria, but an additional 34% are identified by the STEMI-equivalent ST-segment depression criteria with cMRI as the gold standard.

## 7.2 Validation of ECG and biochemical estimates of index acute and final MI sizes

The validation of different biochemical and electrical clinical indices of myocardial infarct size have so far been limited by deficiencies in the gold standards to delineate regions of acute myocardial necrosis and/ or chronic scar in vivo. Infarct size is accurately and reproducibly measured using ceMRI in both acute and chronic phases of myocardial infarction providing an ideal living autopsy (175;176). Using ceMRI to confirm there was a single infarct together with the rise and fall of troponin to confirm acuteness meant that it was possible to precisely define a population with single acute MI. The routinely available biochemical and bioelectrical markers of myocardial infarction both individually and in combination were correlated with the planimetered regions of DE. The treatment with most influence on final infarct size is currently reperfusion therapy based on the presenting ECG, so patients were compared using these subgroups.

Troponin levels are widely available and now accepted as the biomarker of choice in the diagnosis of ACS. Troponin was routinely only measured once at 8-12 hours following onset of chest pain and its primary use is to dichotomise patients into high and low risk. This is illustrated by the TIMI risk scoring system according a single point for positive biomarkers regardless of the value. Troponin is exclusively released from necrotic myocytes so an infarct size derived from troponin levels should not include infarct penumbra such as oedema. Troponin release is a dynamic process over 2 weeks post infarction and the optimum sample timing point is yet to be determined so this study tests the use of the single sample point already in clinical use. The troponin level is likely to be important as an indicator of infarct size and so further aid in risk stratification of patients and therefore clinical decision making.

The standard ECG has been used to detect and estimate MI size for many decades. The Selvester score is a 31 point scoring system based on specific patterns in the QRS complex and provides a simple, economical means of risk stratification at discharge (177). Whilst the Selvester score is straightforward to perform by expert analysts, it is not yet part of routine clinical practice. All the information is available and contained within the ECG and most ECG machines could be adapted to use an algorithm that will provide an automated score.

Acute myocardial injury not only encompasses myocyte damage but also the effects of an acute inflammatory response including oedema. It was thought that ceMRI during the acute phase led to over estimation of infarct size(178) but this has subsequently been demonstrated not to be the case using TTC staining (179;180). It is clear then that the region of DE and TTC are the same but this still does not exclude the likelihood that the distance between necrotic myocytes is expanded in the acute phase due to oedema.

Infarct size has been shown to reduce between the acute and chronic phases of healing by around 30% (181). Of the 57 patients with single AMI, 43 have a scan at visit 1 and visit 2. In these patients the mean reduction in infarct size is from 37 (30) g to 14(14) g or 35%. This early reduction accounts for most of the reduction to a year (40%). Infarct size at 38 days was therefore chosen to represent “final infarct size”, with additional benefit that there were less patients lost to follow up than at later time points. It was hypothesised that there would be a better correlation with infarct size once the acute inflammatory response to injury has settled down.



Patients who received reperfusion therapy had a lower systolic and diastolic blood pressure at the time of ceMRI scan. The trend towards a lower ejection fraction and a difference in secondary prevention prescription may have contributed, although only the rate of ACE inhibitor use was significantly higher (77 vs. 39%).

Nearly  $\frac{3}{4}$  of patients who received reperfusion therapy had ST elevation on the presenting ECG and just under a fifth had ST depression **Table 5-7**. A further 12 % of patients developed ST elevation on repeat ECG testing. The diagnosis of evolving STEMI was missed in 13 % of patients that were not reperfused when the strict ST deviation criteria were applied by the ECG core lab, **4.4 above**. There may also have been better pattern recognition by the core lab than that of the junior doctor assessing the patient in an emergency setting. Of those that were not reperfused, 46% had significant ST depression on the presenting ECG and would be classified as STEMI equivalent.

The patients that were reperfused had larger acute infarct sizes by CKMB, TnI and Selvester score. Infarct sizes were larger by ceMRI measures including total DE area, transmural extent and endocardial extent. Patients who received reperfusion therapy also had larger final infarct sizes by ceMRI at a mean of 38 days **Table 5-8**. There was a significant reduction in mean infarct size for both reperfused and non-reperfused infarcts, -15.4 g and -9.6 g respectively. The greater absolute reduction may be due to resolution of oedema and haemorrhage in reperfused infarcts rather than improved healing of an area of infarction subtended by an open artery. The non-reperfused infarcts more closely reflect the natural history of coronary occlusion and so will not be subject to the same degree of reperfusion injury.

The correlation between a single TnI and area of DE was strong for all infarcts, particularly those that received reperfusion therapy ( $r=0.7$ ,  $p<0.001$ ).

In non-reperfused patients, it has already been shown that TnI correlates poorly with acute infarct size (182), a result that was confirmed in this study. But when TnI is compared to final infarct size in the non-reperfused group the correlation improved from  $r=0.43$  to  $r=0.78$

**Table 5-9.** A similar improvement was seen between Selvester score and acute then final infarct size,  $r=0.31$  to  $r=0.67$  in the non-reperfused patients.

In the reperfused group the trend towards improved correlation between admission biochemical or bioelectrical markers and final infarct size by DE applies to the Selvester score but not TnI. It is not clear why this might be the case.

When considering all infarcts; the correlation between admission TnI and admission DE ( $r=0.70$ ) improves when admission TnI is correlated with final DE ( $r=0.75$ ).

The improvements in correlation were tested by means of a Z test but due to the small study numbers none of the improvements reached significance. The improved correlation between TnI and acute then final infarct size in the non-reperfused group was nearly significant,  $p=0.09$ . Correlations between TnI and geometrical measures of infarct size such as endocardial extent ( $r=0.42$ ,  $p=0.004$ ), number of segments ( $r=0.52$ ,  $p<0.001$ ) and number of slices ( $r=0.53$ ,  $p<0.001$ ) were significant but no better than the total infarct mass.

The rationale for investigating both acute and final infarct sizes by ceMRI is that the area of DE planimetered will be influenced by the timing of the first ceMRI scan, **5.6 above**. The final infarct size at 38 days allows any confounders such as oedema to settle down.

The poor correlation between Selvester score and acute non-reperfused infarct size by ceMRI was surprising ( $r=0.31$ ) as this score was originally designed in the pre-reperfusion era.

However, its use was to estimate chronic infarct size; equivalent to the 10 patients in **Table 5-9** ( $r=0.67$ ,  $p=0.03$ ). Previous investigators into the Selvester score and chronic infarct size by ceMRI have found the best relationships in basal anterior infarcts (183;184) likely due to the limited location of the 6 anterior chest leads and 4 limb leads and infarcts in other locations “hiding” from the ECG. Infarct location was not investigated as a variable in this study due to the small numbers of anterior infarcts and the indiscriminate nature of TnI release. The Selvester score is based on points derived from the QRS complex but the extent of transmuralities did not correlate with the Selvester score.

Multiple linear regression was performed to investigate if the 2 readily available measures of infarct size, TnI and ECG, would improve correlation with ceMRI derived infarct size when used in combination. This hypothesis was based on the premise that TnI indicates the amount of necrotic myocytes and the ECG will account for any additional effects of the infarct process. In the total population the Pearson correlation coefficient increased from  $r=0.71$  to  $r=0.80$  ( $p<0.001$ ). The main contributor was the reperfused group ( $r=0.72$  to  $r=0.82$ ,  $p=0.003$ ). In the non-reperfused group the correlation did improve from  $r=0.28$  to  $r=0.43$  but did not reach significance. Therefore the combination of Selvester and TnI provides an

improved estimate of infarct size in acute reperfused infarcts and again the results are not consistent within the non-reperfused infarct group.

It is not clear why the acute reperfusion strategy should influence the correlation of TnI or Selvester with acute infarct size and is complicated by evidence that reperfusion is itself associated with injury. The kinetics and release ratio of troponins are not well defined and are likely to be affected by reperfusion(24). It has been shown that troponin at 72 and 96 hours correlates well with scintigraphically defined infarct size regardless of reperfusion status (15;16) so it may be that 8-12 hours is too early a sample point. It is unlikely to be too late as troponin levels remain elevated for up to 2 weeks following myocardial injury. The inhomogeneity of the non-reperfused group may contribute and illustrates why studies to investigate the early treatment of patients without ST elevation have been unsuccessful thus far.

In conclusion both biochemical and bioelectrical markers of myocardial infarction provide an estimate of acute infarct size when all infarcts are considered; this correlation is largely driven by the reperfused or STEMI group. TnI measured 8-12 hours post chest pain and Selvester score at mean 64 hours correlate with acute STEMI infarct size by ceMRI and this correlation improves when they are used in combination; but only CKMB correlates with NSTEMI size. When considering the non-reperfused group these markers correlate better with final infarct size. Improved correlation of standard biomarkers with final infarct size suggests that the optimal time for acquiring ceMRI images may be once the acute injury process has settled down.

### 7.3 The detection of myocardial scar by ceMRI in patients with TnI positive chest pain and minimal angiographic coronary artery disease

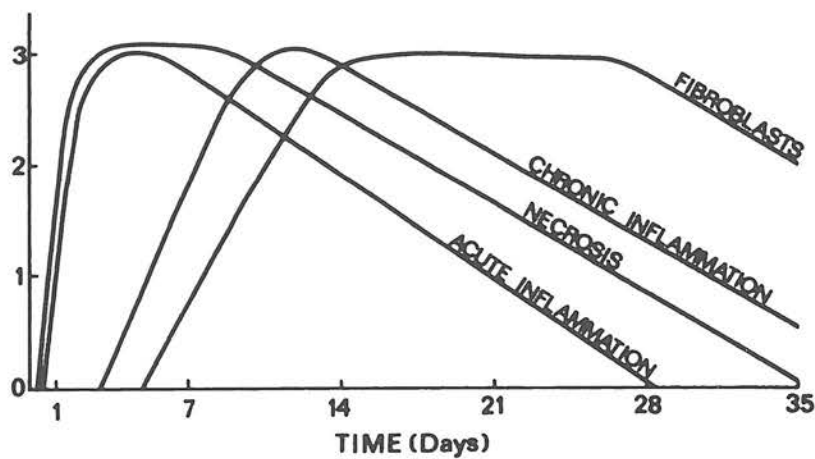
International guidelines recommend early coronary angiography (CA) and revascularisation in all patients diagnosed with acute myocardial infarction. Normal CA does not exclude AMI but makes the final diagnosis less accurate. Christiansen et al. looked at the detection of myocardial scar by ceMRI in patients with TnI positive chest pain and minimal angiographic coronary artery disease in a (non-prospective) group of 23 patients who were referred for ceMRI by their physician, 7 (30%) of which had evidence of DE (185). In this prospective study, 8 (10%) patients with a positive TnI had a normal coronary angiogram and in contrast, 7 (88%) had evidence of DE. The single patient negative for DE had a TnI of 4.4 ng/ml and a final diagnosis (by ceMRI) of Takotsubo cardiomyopathy **5.9 above**. Four out of 7 patients had an ischaemic distribution of DE (2 inferior, 1 lateral and 1 anterior), median TnI of 22 ng/ml and DE mass of 8 g. The remaining 3 had a subendocardial sparing pattern of DE with median TnI 29 ng/ml and DE mass 36.5 g. Therefore the diagnosis of acute myocarditis was made in 43% of patients with positive TnI and normal coronary arteries (cf. 14.2% in the study by Christiansen et al.). Only one patient out of eight (12.5%) had a MACE (stroke) recorded at 3 years and he was from the ischaemic DE group.

It is well recognised that angiographically normal coronary arteries do not exclude coronary artery disease or myocardial infarction, for example recanalisation of an acute thrombotic occlusion or an embolic event. In this group of patients, comprising 10% of all troponin positive patients meeting the inclusion criteria, ceMRI has definitely improved diagnostic certainty. Four (50%) patients were confirmed as a Non STEMI with attendant implications

for prognosis, need for secondary prevention, psychological well being and subsequent occupational and health insurance assessments. Four (50%) patients were spared this label; three with a diagnosis of acute myocarditis and one with Takotsubo cardiomyopathy. These findings require further investigation but illustrate the potential of ceMRI for improving the accuracy of the label (acute) myocardial infarction.

# 7.4 Serial assessment of MI size and characteristics using ceMRI

The natural course of myocardial infarction by ceMRI at 4 time points over 1 year in both reperfused and non-reperfused infarcts (STEMI and NSTEMI) has not been previously documented. Pathological studies are necessarily limited to a single time point per patient but a large autopsy series has shown the histopathological evolution of myocardial infarction in different patients(186) **Figure 7-1.**



**Figure 7-1: Course of time for histopathologic changes in myocardial infarction in man. Ordinate indicates relative severity of histopathologic changes. Reproduced from Fishbein, Chest 1978; 73(6):843-849**

During the first 3-4 days there is infarct expansion due to myocyte necrosis with haemorrhage, oedema and infiltration of leucocytes. At the time of study design the aim was to image the infarct as soon as possible after initial injury so a mean time to scan from chest pain of 2.3 days was acceptable given that there was a reluctance to allow patients with an STEMI out of the coronary care unit to attend a research study for 48 hours post admission, regardless of clinical status.

By 4-6 weeks these changes have largely settled and necrotic cells are no longer detectable, there is functional vascular proliferation, fibroblast infiltration and collagen deposition. The aim of planning scan 2 at 28 days was to correspond with this time point and that which is frequently used in clinical trials.

At 6 months and beyond the acute injury process is complete and myofibroblast activity persists, nourished by the neo vasculature **Table 7-1**. Scans 3 and 4 were planned for 6 months and 1 year to assess the dynamics of infarct healing during this period and to correspond with 2 further time points frequently used in clinical trials. In addition, 4 time points over a year is more than has been used in previous studies and provides a reasonably smooth curve.

**Table 7-1: Relation of age of infarct to vascular and cellular changes**

Age of infarct (days)	Necrosis	Intercellular oedema	Haemorrhage	Vascular proliferation	Neutrophils	Fibroblasts	Collagen
3	+++	++	++	0	+++	0	0
28	+	+	+	+++	0	++	+++
180	0	0	0	++	0	++	+++

All changes graded for severity as follows: 0 absent; + mild; ++ moderate; +++ severe

CeMRI visualises the net effects of factors causing early infarct expansion and subsequent infarct resorption, in a similar way that serial TTC staining on histopathological specimens would. The contrast agent Gd-DTPA is non-specific and remains in the extracellular compartment. Delayed hyperenhancement imaging with ceMRI relies on the different rates of wash in and wash out of GdDTPA between normal and damaged myocardium. In the acute phase of myocardial injury, hyperenhancement is due to loss of cell sarcolemmal integrity. In



the chronic phase the volume of distribution is increased due to the increased interstitial space in collagen. There is therefore no reason why acute and chronic infarcts should appear the same on DE imaging. **Figure 6-2** shows 4 ceMRI scans over 1 year in the same patient with an extensive anterior MI. The reduction in infarct size can be seen but also the clarity of the infarct border improves greatly between scan 1 and scan 2. This is particularly evident on the 2 chamber views (lower panels left and 2<sup>nd</sup> from left).

When considering the 25 patients with single AMI and a complete set of 4 scans the mean reduction in infarct size is 15 (16) g or 36% by 38 days and 17 (16) g or 40% by 1 year. The other measures of infarct geometry in this study, endocardial extent and transmural extent, are also significantly reduced by 1 year confirming that infarct size reduction occurs in all dimensions. This pattern is seen in all infarcts whether reperfused or not meaning that final infarct size is essentially achieved by 38 days. This suggests that final infarct size is achieved outwith the chest pain to scan time of 4 days that encompassed 95% of patients. Imaging for infarct size should not be done during the first week, at least if ceMRI is to be used as a gold standard to test therapies that reduce final infarct size.

MVO, defined by a hypoenhanced core surrounded by hyperenhancement, has been investigated on both early and delayed images. One of the aims of this study was to document the relative incidence of both early and late MVO and its change over time.

When late MVO is present there is always early MVO indicating that they are measuring the same phenomenon. Early MVO is seen more frequently than late MVO (66 vs. 47%,  $p < 0.001$ ). This incidence is higher than the 35% seen with no reflow despite TIMI 3 flow

following primary PCI using intracoronary myocardial contrast echocardiography (187). The size of MVO (9.2 vs. 9.4 g) and percent of infarct size (15 vs. 19%) are similar for early and late MVO respectively. Previous studies have documented MVO resolution by between 6-9 months (67). In this patient population, MVO has largely settled by mean 38 days and in the small number of patients in which it persists the extent is significantly reduced. No patients have late MVO after visit 2 so this information may be used to rule in a recent infarct if biomarkers are normal or determine the culprit infarct site if there are multiple.

The reduction in infarct size was greatest if MVO (early or late) was present on the admission scan. It was anticipated that a reduced blood supply at the microvascular level would impair healing but it is likely that the net effect in infarct resolution as measured by ceMRI is reduction in oedema. It may be that there is more inflammation and "infarct expansion" associated with MVO so that there is a greater rate of regression to the mean by 28 days.

There was a trend to increased rate of reduction in infarct size in reperfused vs. non-reperfused infarcts but again these infarct sizes were significantly larger and the increased rate of change may be due to resolution of the effects of reperfusion injury or haemorrhage into the infarct that caused over estimation during the first week.

In the population of patients with single AMI the mean LV ejection fraction improved by 1.7% at 1 year. There was a significant increase in both LVEDV and LVESV with the main increase between visit 1 and visit 2, continuing at a reduced rate to visit 3. Between visits 3 and 4 there was a general reduction in LV dimension. Overall the mean increase in LVEDV was 23ml (16%) and LVESV 9ml (14%). In the group with late MVO the LVEF remained static

over 1 year but those without late MVO showed a mean increase in LVEF of 5.7%. In the late MVO group, mean LVEDV increased by 38mls (26%) and LVESV by 24ml (32%) whereas in those patients without late MVO, mean LVEDV increased by 8 ml (6%) and LVESV decreased by 7ml (13%).

The mean increase in LV mass was 20g (15%) indicating that there was compensatory hypertrophy as normal myocardium made up for loss of functioning myocardium

The main limitation of this study is the small patient numbers that completed all 4 scans. Due to patient drop outs the complete set of all 4 scans is only available in 25 (44%) patients. The serial analysis did account for this by using the baseline scan as the reference in paired analysis.

This study documents the natural evolution of both reperfused and non-reperfused infarcts at 4 time points over 1 year. The reasons for the patterns of the the rates of change in infarct size over 38 days are not known although it seems to be related to infarct size and associated oedema. Further mechanistic studies to investigate whether there are any therapeutic implications, for example varying arrhythmogenic properties of oedema vs. infarct. Larger studies would be required to investigate the prognostic and therapeutic significance of the change and rate of change of infarct size.

If ceMRI is to be used as a gold standard for infarct size estimation in trials of infarct regeneration such as stem cell therapy it may be more reliable and certainly more practical to measure baseline infarct size at least 2 weeks following AMI and probably at 1 month. The planimetered DE area is unaffected by other factors such as hibernation, stunning or loading conditions and the high spatial resolution means that trials can be adequately powered with

fewer patients. CeMRI is particularly attractive for serial measurements due to the lack of radiation exposure.

The results of this analysis will be of use in providing a “normal range” of infarct evolution against which future therapies that aim to alter infarct size both prospectively and retrospectively may be tested. The study also indicates that the timing of the ceMRI scan will be of great importance in study design.

## 7.5 CRP in the detection of higher risk patterns of AMI

There is an acute inflammatory response to myocardial injury but the precise trigger is as yet unknown(188). CRP is a non-specific inflammatory marker that appears to be a strong predictor of cardiovascular risk (189), including in patients with ACS (132). It is currently unclear whether inflammatory markers measurable in the peripheral blood can be clinically useful tools for risk assessment and whether intervention to reduce inflammation will influence risk (190). Further information on the association of CRP with acute myocardial necrosis may help to guide future therapeutic trials. CeMRI was used to investigate the relationship between CRP and the diagnosis and prediction of infarct size. In the investigation into whether the measurement of CRP in troponin positive patients can predict the presence of MVO comparisons were made with the standard diagnostic armourey.

In this study a single CRP was checked at the time of the first ceMRI scan at a mean (SD) of 55 (32) hours, the time point when CRP will have peaked and reached a plateau. ROC analysis of the total population showed that measuring CRP at this time has a diagnostic accuracy close to CK (AUC 0.8 vs. 0.86, **Figure 5-8**). The AUC for TnI is shown for comparison and is near perfect at 0.98.

An elevated CRP is a sensitive but not specific test for myocardial damage that becomes more discriminating as the value increases. The higher of the previously investigated CRP cut offs was used in the analysis. In addition the 10mg/L cut off point chosen for the initial analysis has been shown to be associated with hard end points and approximates the median (7.3mg/L) of this study population. A CRP of  $10 \geq$  mg/L in this study population provided a sensitivity of 0.74 and specificity of 0.63 for the diagnosis of myocardial infarction. This does

not suggest that CRP should be used as an alternative to current biomarkers in the diagnosis of acute myocardial damage but demonstrates that CRP release is triggered by infarction. Patients with a high CRP have larger infarcts by TnI and DE planimetry and greater endocardial extent but no difference in transmural extent.

Patients with a high CRP showed a trend towards a lower mean acute ejection fraction (54 % vs. 60.5 %) that reaches significance at 6 months (53% vs. 63 %,  $p=0.001$ ). The mean change in LVEF during the remodelling process showed opposite polarity in the high CRP group (-1.6%) to the low CRP group (+2.9%). In keeping with previous studies (191) there was a moderate negative correlation between CRP and acute left ventricular ejection fraction in reperfused infarcts ( $r=-0.49$ ,  $p=0.004$ ). The correlation was better with LVEF at 6 months ( $r=-0.67$ ,  $p<0.0001$ ) which may explain the association with adverse outcome and improve identification of those higher risk patients that would benefit from intensification of asecondary prevention therapies.

Using ceMRI as the gold standard for infarct size in patients with single AMI there is a moderate correlation with CRP in the total population ( $r=0.57$ ,  $p<0.001$ ), in reperfused ( $r=0.6$ ,  $p<0.001$ ) and in non-reperfused ( $r=0.56$ ,  $p=0.004$ ) infarcts **Figure 5-9, Table 5-17**.

The white cell count does not correlate with reperfused infarct size ( $r=0.2$ ) but shows a modest but significant correlation with infarct size in the non-reperfused group ( $r=0.55$ ). The results in the non-reperfused infarct group are better with both markers of inflammation than between TnI and infarct size ( $r=0.39$ ) but not significantly so ( $p=0.5$ ). It appears that reperfusion therapy has an effect on the relationship between inflammation and myocyte

necrosis and a larger study group would be required to investigate whether CRP (or WCC) truly gives a better estimate of infarct size than TnI in the non-reperfused (NSTEMI) group of patients.

The absolute reduction in median infarct size between admission and 38 days in patients with CRP >10mg/L was 12 g which was significantly greater than the median reduction in infarct size in the low CRP group, 6.5 g,  $p=0.025$ . When the cutoff of 26 mg/L was used the difference in median reduction in infarct size was greater; 18.5 vs. 6 g,  $p=0.013$ . These results are in keeping with the hypothesis that overestimation of infarct size in the acute phase of myocardial injury by ceMRI may be due to the associated inflammatory response. The early infarct expansion may be related to the inflammatory response in the myocardial tissue with oedema being the main contributor and will have settled by 38 days. The acute CRP levels were therefore correlated with final infarct size and there was a reduced correlation in the reperfused group (from  $r=0.6$  to  $r=0.4$ ) but increased in the non-reperfused group (from  $r=0.56$  to  $r=0.87$ ). It is not possible to say why this difference occurred but this polarisation may be influenced by different healing characteristics or inflammation associated with reperfusion injury.

Seventy percent of patients with a high CRP have early MVO compared to 29 % with a low CRP,  $p=0.011$ . Similarly, 47% patients with a high CRP have late MVO compared to 7% in the low CRP group,  $p=0.01$ .

To investigate potential mechanisms for CRP determining cardiovascular risk in addition to that of TnI, the sensitivity and specificity of CRP in the diagnosis of MVO was assessed. The

AUC for early MVO is 0.69 and for late MVO is 0.75. Using a CRP cut off of 3 mg/L there is a similar sensitivity and specificity in the detection of early (0.97, 0.16) and late (1.0, 0.19) MVO. Using a CRP cut off of 10 mg/L there is again a similar sensitivity and specificity in the detection of early (0.87, 0.38) and late (0.95, 0.4) MVO. Overall there is minor loss of sensitivity but greatly improved specificity when using the higher cut point of 10 mg/L. It seems likely that use of late MVO is more robust than early MVO although they are part of the same spectrum of no reflow. Late MVO was therefore used in the further analysis as indicates a more profound level of reduced tissue perfusion demonstrated by the 11 patients that have early MVO that fills in by 10 minutes.

The most reliable biomarker in the detection of late MVO was CK at a cut off of 850 IU (sensitivity 0.9 and specificity 0.8). A patient with a CK >850 and ACS is more than 4 times as likely as not to have late MVO by ceMRI.

The next best was the ECG derived Selvester score with a cut off of 3.5 (equivalent to infarct size >9% LV mass) which had sensitivity of 0.75 and specificity of 0.8.

The optimum CRP was 26mg/L with a sensitivity of 0.85 and specificity 0.66. A patient with symptoms of ACS who is TnI positive and has a CRP >26 is more than twice as likely to have microvascular obstruction. A similar result was obtained with TnI (cut off 25 ng/ml) making it unlikely that the risk due to a high CRP over and above TnI is due to a different frequency of MVO.

Logistic regression was then performed to assess which biomarkers were the best in the prediction of late MVO. The only 3 left in the model were CK, CRP and Selvester score. The



3 patients with CRP <26 and late MVO all had a CK of above 850 IU so the combination of the 2 would have meant the sensitivity was 1.0. Infarct size by ceMRI was not included as it would not be applicable to a broader clinical population without access to ceMRI. If it were included then it becomes the strongest predictor of presence of MVO. It is not possible to control for the effects of infarct size so it may be that this is simply what CRP is measuring.

CRP is easily and inexpensively measured and standardised high sensitivity assays are available commercially. The measurement of CRP will not replace TnI or CK for the diagnosis of ACS but has been shown in large epidemiological studies to provide additive information. Using ceMRI as a gold standard for infarct presence, size and MVO; a CRP > 10mg/L corresponds with a higher risk group and has a sensitivity of 0.74 and specificity of 0.63 in the diagnosis of AMI.

CRP correlates with recognised prognostic indicators such as LV structure, function and infarct size regardless of acute reperfusion status. A CRP of >26 mg/L means a patient with ACS is more than twice as likely to have MVO and in combination with CK will correctly identify 88% of patients.

The association of MVO with infarct size is so strong that it was not possible to determine if MVO was associated with an additional inflammatory response. It may be that CRP is the bridge between infarct size and morphology.

## 7.6 MMP-1 promoter polymorphisms and changes in LV volume following AMI

The present data suggest that there may be an association between the MMP-1 promoter genotype and the risk for remodelling after AMI. It is biologically plausible that MMP-1 promoter polymorphisms might influence remodelling. The insertion of a G nucleotide in the promoter region of the MMP-1 gene determines the presence of an Ets binding site, which increases the transcription of MMP-1 in many cell types (156). MMP-1 is the most ubiquitous interstitial collagenase and plays a vital role in the degradation of fibrillar collagens. These are the predominant structural proteins in the human myocardium (150), and collagen degradation is a hallmark of early remodelling. This is associated with increased myocardial expression of MMP-1 and its messenger ribonucleic acid, plus increases in circulating levels (153-155). In addition, in a murine model, the introduction of the human MMP-1 gene results in LV dilation and dysfunction (151). MMP-1 polymorphisms have also been implicated in the progression of other disease states, particularly cancer. For example, MMP-1 is found in multiple tumor cell types, and several studies have suggested that the GG allele is associated with an increased risk for malignancy and a greater risk for invasion and metastatic spread (192).

Patients possessing 2 GG alleles seem to be at greatly increased risk for remodelling, whereas heterozygotes, possessing 1 G and 1 GG allele, appear at no increased risk. This is consistent with previous reports. These have demonstrated a particularly large incidence of GG homozygotes in many tumor cell lines (157), plus an association between GG/GG genotype and the invasiveness of malignant melanoma and increased risk for colorectal and renal carcinoma (193-195). In addition, a significant association has been demonstrated between MMP-1 GG/GG genotype and lung carcinoma, even after adjustment for age, gender, and

smoking status (196). Interestingly, the excess risk was particularly pronounced in men with the GG/GG genotype(196), an observation that has also been made in patients with renal carcinoma (195). One potential explanation may be that MMP-1 activity is inhibited by ovarian steroids (197). This may also partly explain why the men in this cohort with GG/GG genotype exhibited such marked remodelling.

There are a number of limitations in this study including the absence of any direct evidence that possession of the MMP-1 GG/GG polymorphism is associated with enhanced translation into functional MMP-1 or increased collagenolytic activity after AMI. Likewise, there is no data regarding the activity of other MMPs and tissue inhibitors of metalloproteinases in this setting. The use of ceMRI to define LV volumes greatly reduces sample size requirements (198) but the small number of patients, especially homozygotes for the GG allele, limits the conclusions that can be drawn. This is particularly true given the unexpected finding that patients with the GG/GG genotype experienced greater LV dilation despite an absence of anterior AMI in this subgroup. Further work is required to address these important limitations and confirm an association between homozygosity for the MMP-1 GG allele and LV remodelling.

## 7.7 Additional findings by ceMRI

Myocardial infarction has proved to be one of the most frequently missed clinical diagnoses in comparison with autopsy findings (199;200). Small subendocardial scar detected by ceMRI is missed by nuclear scintigraphy (71), ECG, or segmental wall motion (60) on echocardiography. Histopathological studies give credence to the idea that any region of myocardial scarring has the potential to adversely affect prognosis either by heart failure or dysrhythmias (201).

The current tools available to the clinician looking after a patient with chest pain syndrome include the history and examination, ECG, TnI, echocardiography and coronary angiography. These methods are not able to directly visualise myocardial damage, whilst ceMRI is.

The presence of any DE may be a marker of the burden of coronary atherosclerosis (202) that is the predisposing cause of acute cardiac events from a post mortem series of sudden death victims without known heart disease (203;204). The majority of these cases have areas of healed myocardial necrosis (205) that could be identified on ceMRI.

The presence of DE is the strongest multivariable predictor of MACE and cardiac mortality compared with common clinical measures such as ECG and LV function. A threshold was demonstrated and even a small myocardial scar (<2% LV mass) was associated with a > 7 fold increase in MACE (206). Thus suggesting that DE provides, “complementary and incremental associations with MACE and cardiac mortality beyond the currently available to clinical tools on the assessment of a patient with chest pain”.

Within a group of patients admitted with first episode of chest pain 37% had a single acute MI by a combination of ceMRI and biomarkers. The remaining patients are at lower risk by

conventional measures **Table 5-1**. Delayed hyperenhancement was detected in a further 18 % of patients.

### **Acute myocarditis**

Three patients (4% of TnI positive group) that may have been incorrectly diagnosed with ACS by conventional diagnostic tools have been correctly identified using ceMRI. Confidence in the pattern of distribution of mid wall DE may in future prevent the need for inpatient angiography in these patients. This small series suggests that the extent of DE does reduce with time but is seen to persist for at least one year. The recognition of the two distributions of DE is useful in differentiating ischaemic from non ischaemic myocardial damage. The subendocardial sparing of DE is non-specific and has been described in a number of conditions: myocarditis(160); sarcoidosis (72); amyloidosis (207) ; dilated cardiomyopathy(202); hypertrophic cardiomyopathy(208); and chronic renal failure(209). Additional clinical information is therefore required if ceMRI suggests that there is myocardial involvement.

### **Prior myocardial infarction**

Twenty (13%) patients had evidence of previous myocardial infarction when examined using ceMRI; 11 were TnI positive and nine were TnI negative.

Only 4 (20%) patients would have been identified as prior infarction by the presence of Q waves confirming the lack of sensitivity of this marker. The development of Q waves requires a critical extent of scar (114;221) and myocyte necrosis often exists without significant Q waves (60;222). The reverse is also true as Q waves are known to occur in conditions other than MI (223-225). Two patients that were troponin negative and DE positive had a normal ECG and 2 met criteria for LVH, the remaining 5 had suspicious ECG patterns. The opinion of an ECG

core laboratory represents a lower negative ECG rate than would be achieved by the general physician that looks after TnI negative patients in current clinical practice. Only 1 patient would have been identified as prior MI by the presence of Q waves confirming the lack of sensitivity of this marker.

### **Troponin I positive patients**

Eleven patients (14%) from the 80 that were TnI positive had evidence of previous myocardial infarction when examined using ceMRI. It should be noted that all patients recruited had what they report as first episode of chest pain, the implication in this population is that the infarcts were silent, which highlights the limitations of relying on the patient history that is necessarily subjective. Different ceMRI sequences may assist in determining infarct age but these were not clinically validated at the time of the study. It may be that the presence of early MVO can assist in the confirmation of an infarct being <28 days old which may be of clinical use, for example in deciding culprit vessel for percutaneous coronary intervention. In one case the improved spatial resolution of ceMRI over standard transthoracic echo has identified severely thinned and aneurysmal segment of LV myocardium that would merit long term follow up.

### **Troponin I negative patients**

Nine patients (12%) out of the 73 with a negative TnI had evidence of prior MI by ceMRI. Twenty five percent of these patients underwent diagnostic coronary angiography which is a significantly lower proportion than is currently recommended for patients with MI. This figure may even be artificially elevated due to the potential influence of the ceMRI result on clinician decision-making.

Only a third of these patients with a negative troponin in the presence of DE were discharged on adequate secondary prevention therapy. This result raises the possibility of a potential forgotten population when compared to the population with single AMI where secondary prevention was prescribed to over 85%.

The second patient example showed a small subendocardial rim of DE but normal coronaries in a patient with severe dilated cardiomyopathy. This pattern of DE has been previously described in patients with DCM but usually in the mid wall. It is possible there was previous plaque rupture or side branch occlusion that was not distinguishable on standard coronary angiography. The extent of DE was small so it remains likely that the aetiology of DCM in this patient was alcohol.

Silent myocardial ischaemia is defined as objective documentation of myocardial ischaemia in the absence of angina or angina equivalents. Since its original description in the 1970s it had undergone extensive investigation and the clinical significance is now well established. If an exercise tolerance test is performed on an asymptomatic population up to 8 % will have abnormal ETT and 3 % will have significant coronary disease (210;211). Post MI, the reported frequency of silent ischaemia is 30 - 43% and ongoing ischaemia ( silent or not) is associated with an increased risk of infarction and death (212). The prognosis of patients with unrecognised MI is comparable or worse than recognised MI (213;214). The frequency of myocardial scars in the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) population by ceMRI was 29% (72/248) in Swedish 70 year olds. Twenty percent (49/248) had unrecognised MI, 5 % (12/248) had another pattern of DE and 4% (11/248) had a history of MI (215).

There were an additional 5 patients that were TnI negative had evidence of delayed hyperenhancement that spared the subendocardium **Prior non-ischaemic fibrosis, below.** Therefore the incidence of myocardial fibrosis that would only be detected by ceMRI was 25/153 (16%) of patients admitted to hospital to rule out myocardial infarction when presenting for the first time with chest pain. This myocardial fibrosis will presumably carry an adverse prognostic risk that would otherwise be unrecognised.

### **Prior non-ischaemic fibrosis**

Five patients (7%) out of 73 that were TnI negative had evidence of DE that spared the subendocardium. In all of these patients it was localised to the basal lateral segments. These patients had evidence of myocardial scarring that will carry an adverse prognostic risk. Further work is required to investigate the implications of an incidental discovery of “non-ischaemic” fibrosis. It was only possible to suggest aetiology in the patient example and that was severe LVH (illustrated in **figure 6.20**). This patient had experienced a sudden death at 3-year case note review.

### **Minimal myocyte necrosis**

Nine patients (11%) out of 80 that were TnI positive had no evidence of DE on ceMRI. The threshold TnI value of 4.4 ng/ml may be useful in refining the term ACS. It has been shown as that any elevation of troponin is associated with adverse risk (216-219) and that future risk does relate to extent of troponin release (220). Patients that are TnI positive but DE negative may be used to define the group of patients with minimal myocyte necrosis described by Fox et al. who used an arbitrary cut off troponin T value of 1.0 for the label, “ACS with minimal myocyte necrosis” (168). The term “necrosette” has been used to describe those patients that



are CK negative but troponin positive. The serum troponin levels are only elevated for at most 2 weeks after the acute phase of myocardial injury so ceMRI will allow the detection of small myocardial scar caused by subclinical coronary events out with this window.

Two patients in this group had a CK value greater than twice upper limit of normal. One had Takotsubo's cardiomyopathy and the other with severe LVH. It may follow that absence of visible scar is associated with reduced future risk, and so improve risk stratification. There are a number of potentially confounding reasons for the ceMRI being false negative for DE. These include: the interslice gap of 2mm, patient movement (e.g. during respiration), and scan quality e.g. myocardium inadequately "nulled", and artifact. Ultimately presence or absence of DE in this study was determined by visual inspection so misinterpretation or human error may play a role. This could be improved by the use of pixel intensity threshold software, an option not available in the unit at the time of post processing.

On reviewing the basic clinical data (including transthoracic echo) for the patient with Takotsubo's cardiomyopathy the diagnosis could have been made without the use of ceMRI. However, ceMRI confirmed that there was no visible scarring. This case also highlights the benefits to patients of being part of a clinical trial with the associated increased scrutiny of data.

### **Unstable angina**

Eleven patients (15%) patients out of the 73 who were admitted with ischaemic chest pain and a normal troponin were diagnosed with unstable angina. The diagnosis in this population required additional objective evidence for lack of MI (absent DE) and coronary disease

(dynamic ST segment deviation, significant stenosis at coronary angiography (or coronary spasm) or positive inpatient exercise test).

### **Chest pain, other**

Forty eight patients (65%) out of the 73 patients admitted with ischaemic chest pain and a normal troponin had no evidence of myocardial involvement when ceMRI is used in addition to standard diagnostic investigations. Thirty patients (41%) were discharged without a specific diagnosis, i.e. "chest pain, unknown cause".

They were younger and there was a higher proportion of females when compared to single AMI. This figure was at the lower end of the previously described spectrum ranging from 40 % (226) to 70% (227) and may have been influenced in part by the increased sensitivity of ceMRI in providing additional diagnostic information.

### **RV infarction**

RV infarction can complicate up to half of inferior myocardial infarctions (228). RV infarction syndrome covers a wide spectrum of presentations and defines a higher risk population of patients. The diagnosis of RV infarction is largely made clinically on based on the findings of hypotension, a raised JVP and clear lung fields in the context of an inferior STEMI. ST elevation on the right sided precordial leads of an ECG will be of use if performed early enough. The RV is not usually adequately visualised by TTE to identify regional wall motion abnormality. The treatment is quite specific and contrary to standard LV infarction management with mainstay being fluid loading if there are no revascularisation issues. In this population ceMRI identified 12 patients with RV infarction accounting for 33% of all inferior AMIs, both STEMI and NSTEMI. RV function was reported as normal in all standard TTEs

that were performed as part of the post AMI protocol. CeMRI has non invasively identified an important complication of inferior myocardial infarction that was not apparent on routine TTE. Even if the condition were subclinical, closer attention to fluid balance and more cautious introduction of hypotensive medication would be warranted.

### **LV thrombus**

Studies from the pre- and early reperfusion eras reported that LV thrombus occurred in 15 - 56% of anterior AMIs. Contemporary studies suggest a lower overall incidence in general of around 4% and within the anterior AMI subgroup the incidence approaches 10% (229-232). In this study of patients first presentation of chest pain the incidence of LV thrombus is 6.25% of all troponin positive patients. Of those with an anterior AMI the incidence rises to 19%. These patients were a group with large infarcts due to occlusion of the proximal LAD. They are therefore a high risk group and mean LVEF was <40%. All 5 patients underwent routine TTE and although the potential substrate was identified there were no confirmed sightings of thrombus. There is debate as to the actual incidence of embolic events but it is difficult to ignore once seen. Formal anticoagulation is not part of routine clinical protocol unless thrombus is seen. In all 5 patients a short course of warfarin was commenced based on the ceMRI findings and at the 6 month follow up scan no thrombus was detected.

## 8 Conclusions

This study has demonstrated that it is possible to perform ceMRI on patients admitted with chest pain within one week of admission and that it is safe to do so.

The presenting ECG in patients with no historical or ECG evidence for previous AMI detects only 50% of the AMIs using the ACC/ESC STEMI criteria, but an additional 34% are identified by the STEMI-equivalent ST-segment depression criteria with ceMRI as the gold standard.

In patients diagnosed with myocardial infarction it is possible to estimate infarct size using either TnI measured at 8-12 hours following onset of chest pain or the ECG using the Selvester score at discharge. The addition of Selvester score to TnI improves the correlation with ceMRI derived AMI size in reperfused infarcts (STEMI).

The correlation of infarct size by TnI or Selvester score shows a trend to improvement when compared to ceMRI performed mean 38 days after AMI. This may be a more reliable time point at which to measure infarct size by planimetry if this is to be used as a surrogate end point in future studies.

Ten percent of patients that were TnI positive had a normal coronary angiogram, 88% of whom had DE. 37% these patients with DE had subendocardial sparing suggesting acute myocarditis.

A natural history of infarct evolution is described for patients that received urgent reperfusion therapy (STEMI) and those who did not (NSTEMI). There is a mean reduction in infarct size

of 35 % that predominantly occurs between admission and a mean of 38 days. The rate of change in infarct size remains stable thereafter to 1 year and final reduction in infarct size is 40%. The presence of late MVO is associated with a greater absolute reduction in infarct size and an increase in LV dimensions.

CRP provides information that is comparable to CK in the diagnosis of AMI and has a moderate correlation with acute infarct size regardless of acute reperfusion status and with LV ejection fraction at 6 months. CRP has a modest sensitivity and specificity for the detection of MVO. A patient with ACS and a CRP of >26 mg/L is more than twice as likely to have MVO and in combination with CK of  $\geq 850$  IU/ml will correctly identify 88% of patients.

Patients possessing 2 GG alleles in the MMP-1 promoter sequence were at increased risk for remodelling compared with homozygotes for the G allele and heterozygotes possessing 1 G and 1 GG allele.

Thirty seven percent of patients with first hospital admission with chest pain had a single AMI by a combination of bioelectrical, biochemical and biomagnetic markers. A further 16% had evidence of previous myocardial scarring in the absence of prior significant, recognisable symptoms. Nine percent of TnI positive patients had no evidence of myocardial scar by ceMRI. Additional findings included RV infarction in 8%, LV thrombus in 3% and acute myocarditis in 2%.

This thesis illustrates that advanced imaging of a broad population using ceMRI can improve the diagnostic yield of acute and prior myocardial scarring due to ischaemic or non ischaemic aetiology. Infarct size can be estimated using biomarkers of myocyte necrosis and

inflammation together with bioelectrical markers. In terms of infarct size the dichotomy between STEMI and NSTEMI is artificial and there is considerable overlap between the 2 groups and **Figure 8-1** demonstrates that infarct size is a continuum. Further work is required to identify the characteristics of patients presenting with NSTEMI, such as ST deviation, who would derive similar benefit from an early reperfusion strategy rather than being treated conservatively with at most aspirin, clopidogrel and heparin on a medical ward.

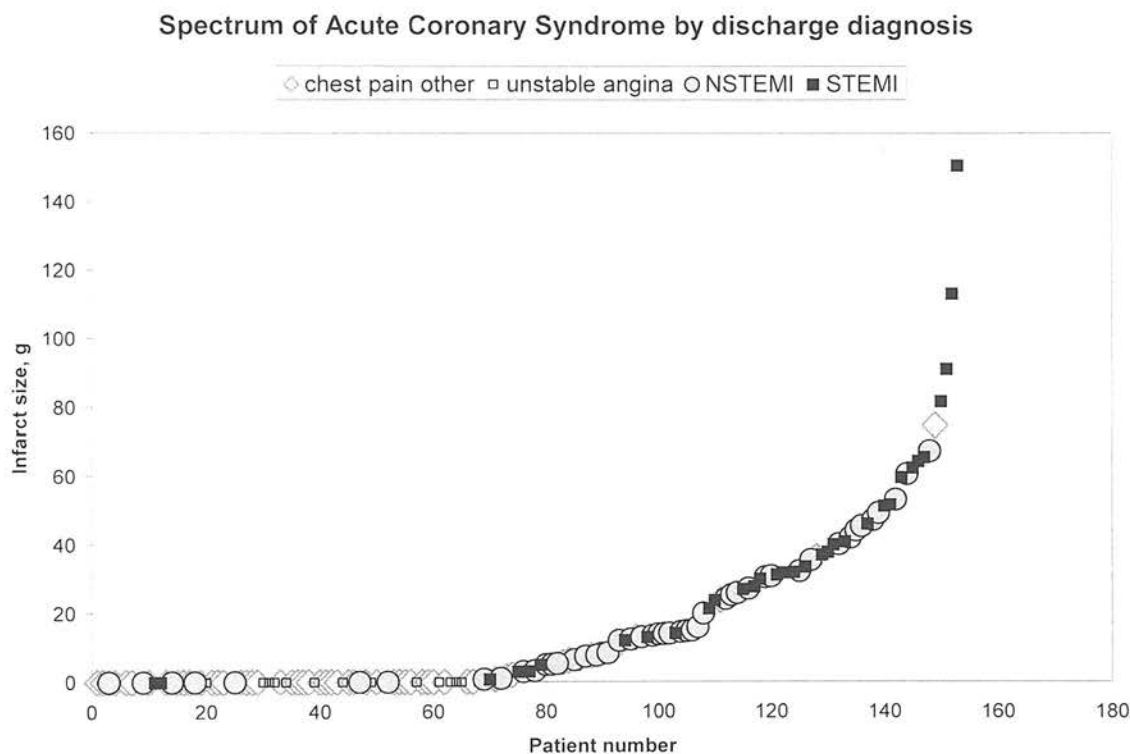


Figure 8-1: Ranked infarct sizes for each patient

## 9 Further studies

The advocacy of the routine use of ccmrI in patients admitted with chest pain should be further investigated with larger studies to identify the potential forgotten population of patients with missed prior or mis-labeled myocardial infarction that will provide both prognostic and cost effective information.

To refine immediate risk stratification by the ECG on presentation the contribution of an increase in the number of leads and/or electrodes, T-wave changes, and ST-segment changes appearing in serial ECG recordings should be investigated. Addition of selected leads such as V4R, V7, or V8 (233) or multi-lead body surface maps (234) have been shown to increase sensitivity. However, the ability to increase sensitivity via additional electrodes must be confirmed when “ST-segment deviation” replaces “ST segment elevation” in AMI criteria for the standard 12-lead ECG.

The use of CRP in the detection of microvascular obstruction requires further investigation, in particular to investigate the role of inflammation in MVO and to test if anti-inflammatory therapies are effective.

Further investigation into the international reproducibility of the DE image acquisition and analysis are ongoing.

Continued work with biomarkers will include investigations into NtBNP and infarct size/ characteristics and LV remodeling. In addition the analysis of troponin degradation products will be assessed as a means of predicting hibernating or stunned myocardium and MVO (235).

## 10 Study Limitations

This study is limited to the population of patients with their first episode of chest pain, who have been deemed to be at enough risk to merit hospital admission. The patients had to be clinically stable following initial treatment and motivated enough to participate in a study that involved an hour long ceMRI scan. The application to a broader population therefore needs to be assumed with consideration.

Using single observer image analysis for the gold standard of infarct size was not ideal but necessary. Any subjective difficulties of image interpretation were settled by arbitration (BAG). A complete ceMRI assessment of a patient with ischaemic heart disease would require more information on viability and myocardial perfusion particularly in those patients that were delayed enhancement negative.



# 11 References

## Reference List

- (1) Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999; 353(9164):1547-1557.
- (2) Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; 90(1):583-612.
- (3) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (4) British Heart Foundation. British Heart Foundation 2006 Coronary Heart Disease Stats. 2006.  
Ref Type: Internet Communication
- (5) Information Services Department annual report on Coronary Heart Disease. 31-10-2006.  
Ref Type: Generic
- (6) Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974; 54(6):1496-1508.
- (7) Wilson RF, Laxson DD, Lesser JR, White CW. Intense microvascular constriction after angioplasty of acute thrombotic coronary arterial lesions. *Lancet* 1989; 1(8642):807-811.
- (8) Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J* 2001; 22(9):729-739.
- (9) Geltman EM, Ehsani AA, Campbell MK, Schechtman K, Roberts R, Sobel BE. The influence of location and extent of myocardial infarction on long-term ventricular dysrhythmia and mortality. *Circulation* 1979; 60(4):805-814.
- (10) Chapman BL. Correlation of mortality rate and serum enzymes in myocardial infarction. Test of efficiency of coronary care. *Br Heart J* 1971; 33(5):643-646.

- (11) Roberts R, Husain A, Ambos HD, Oliver GC, Cox JR, Jr., Sobel BE. Relation between infarct size and ventricular arrhythmia. *Br Heart J* 1975; 37(11):1169-1175.
- (12) Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J, Jr. et al. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation* 1971; 43(1):67-82.
- (13) Roberts R, Henry PD, Sobel BE. An improved basis for enzymatic estimation of infarct size. *Circulation* 1975; 52(5):743-754.
- (14) Katus HA, Diederich KW, Schwarz F, Uellner M, Scheffold T, Kubler W. Influence of reperfusion on serum concentrations of cytosolic creatine kinase and structural myosin light chains in acute myocardial infarction. *Am J Cardiol* 1987; 60(7):440-445.
- (15) Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. *Heart* 2002; 87(6):520-524.
- (16) Remppis A, Ehlermann P, Giannitsis E, Greten T, Most P, Muller-Bardorff M et al. Cardiac troponin T levels at 96 hours reflect myocardial infarct size: a pathoanatomical study. *Cardiology* 2000; 93(4):249-253.
- (17) Selvester RH, Wagner GS, Hindman NB. The Selvester QRS scoring system for estimating myocardial infarct size. The development and application of the system. *Arch Intern Med* 1985; 145(10):1877-1881.
- (18) Palmeri ST, Harrison DG, Cobb FR, Morris KG, Harrell FE, Ideker RE et al. A QRS scoring system for assessing left ventricular function after myocardial infarction. *N Engl J Med* 1982; 306(1):4-9.
- (19) De Sutter J, Van De WC, Gheeraert P, De Buyzere M, Gevaert S, Taeymans Y et al. The Selvester 32-point QRS score for evaluation of myocardial infarct size after primary coronary angioplasty. *Am J Cardiol* 1999; 83(2):255-7, A5.
- (20) Clemmensen P, Grande P, Saunamaki K, Wagner NB, Selvester RH, Wagner GS. Evolution of electrocardiographic and echocardiographic abnormalities during the 4 years following first acute myocardial infarction. *Eur Heart J* 1995; 16(8):1063-1069.
- (21) Ideker RE, Wagner GS, Ruth WK, Alonso DR, Bishop SP, Bloor CM et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarcts. *Am J Cardiol* 1982; 49(7):1604-1614.
- (22) Roark SF, Ideker RE, Wagner GS, Alonso DR, Bishop SP, Bloor CM et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. III. Correlation with quantitative anatomic findings for inferior infarcts. *Am J Cardiol* 1983; 51(3):382-389.

- (23) Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. *Circulation* 1990; 82(5):1847-1853.
- (24) Gibbons RJ, Valeti US, Araoz PA, Jaffe AS. The quantification of infarct size. *J Am Coll Cardiol* 2004; 44(8):1533-1542.
- (25) Prigent F, Maddahi J, Garcia EV, Resser K, Lew AS, Berman DS. Comparative methods for quantifying myocardial infarct size by thallium-201 SPECT. *J Nucl Med* 1987; 28(3):325-333.
- (26) Prigent FM, Maddahi J, Van Train KF, Berman DS. Comparison of thallium-201 SPECT and planar imaging methods for quantification of experimental myocardial infarct size. *Am Heart J* 1991; 122(4 Pt 1):972-979.
- (27) Grande P, Hindman NB, Saunamaki K, Prather JD, Hinohara T, Wagner GS. A comprehensive estimation of acute myocardial infarct size using enzymatic, electrocardiographic and mechanical methods. *Am J Cardiol* 1987; 59(15):1239-1244.
- (28) Kang X, Berman DS, Van Train KF, Amanullah AM, Areeda J, Friedman JD et al. Clinical validation of automatic quantitative defect size in rest technetium-99m-sestamibi myocardial perfusion SPECT. *J Nucl Med* 1997; 38(9):1441-1446.
- (29) O'Connor MK, Gibbons RJ, Juni JE, O'Keefe J, Jr., Ali A. Quantitative myocardial SPECT for infarct sizing: feasibility of a multicenter trial evaluated using a cardiac phantom. *J Nucl Med* 1995; 36(6):1130-1136.
- (30) Fieno DS, Thomson LE, Slomka P, Abidov A, Friedman JD, Germano G et al. Quantitation of infarct size in patients with chronic coronary artery disease using rest-redistribution Tl-201 myocardial perfusion SPECT: correlation with contrast-enhanced cardiac magnetic resonance. *J Nucl Cardiol* 2007; 14(1):59-67.
- (31) Mahrholdt H, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation* 2002; 106(18):2322-2327.
- (32) Hedstrom E, Palmer J, Ugander M, Arheden H. Myocardial SPECT perfusion defect size compared to infarct size by delayed gadolinium-enhanced magnetic resonance imaging in patients with acute or chronic infarction. *Clin Physiol Funct Imaging* 2004; 24(6):380-386.
- (33) Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100(19):1992-2002.
- (34) Tracy RP. Inflammation in cardiovascular disease: cart, horse or both--revisited. *Arterioscler Thromb Vasc Biol* 2002; 22(10):1514-1515.

- (35) Michaels AD, Gibson CM, Barron HV. Microvascular dysfunction in acute myocardial infarction: focus on the roles of platelet and inflammatory mediators in the no-reflow phenomenon. *Am J Cardiol* 2000; 85(5A):50B-60B.
- (36) Braunwald E. Application of current guidelines to the management of unstable angina and non-ST-elevation myocardial infarction. *Circulation* 2003; 108(16 Suppl 1):III28-III37.
- (37) Dargie H. Myocardial infarction: redefined or reinvented? *Heart* 2002; 88(1):1-3.
- (38) Grazia MM. Acute myocardial infarction--are women different? *Int J Clin Pract* 2005; 59(1):2-5.
- (39) Patel H, Rosengren A, Ekman I. Symptoms in acute coronary syndromes: does sex make a difference? *Am Heart J* 2004; 148(1):27-33.
- (40) Kannel WB, Cupples LA, Gagnon DR. Incidence, precursors and prognosis of unrecognized myocardial infarction. *Adv Cardiol* 1990; 37:202-14.:202-214.
- (41) Sheifer SE, Manolio TA, Gersh BJ. Unrecognized myocardial infarction. *Ann Intern Med* 2001; 135(9):801-811.
- (42) Bellenger NG, Grothues F, Smith GC, Pennell DJ. Quantification of right and left ventricular function by cardiovascular magnetic resonance. *Herz* 2000; 25(4):392-399.
- (43) Wu E, Judd RM, Vargas JD, Klocke FJ, Bonow RO, Kim RJ. Visualisation of presence, location, and transmural extent of healed Q-wave and non-Q-wave myocardial infarction. *Lancet* 2001; 357(9249):21-28.
- (44) Edelman RR, Wallner B, Singer A, Atkinson DJ, Saini S. Segmented turboFLASH: method for breath-hold MR imaging of the liver with flexible contrast. *Radiology* 1990; 177(2):515-521.
- (45) Simonetti OP, Kim RJ, Fieno DS, Hillenbrand HB, Wu E, Bundy JM et al. An improved MR imaging technique for the visualization of myocardial infarction. *Radiology* 2001; 218(1):215-223.
- (46) Pennell DJ, Sechtem UP, Higgins CB, Manning WJ, Pohost GM, Rademakers FE et al. Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. *Eur Heart J* 2004; 25(21):1940-1965.
- (47) Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100(19):1992-2002.

- (48) Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med* 2000; 343(20):1445-1453.
- (49) Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. *J Am Coll Cardiol* 2000; 36(6):1985-1991.
- (50) Hillenbrand HB, Kim RJ, Parker MA, Fieno DS, Judd RM. Early assessment of myocardial salvage by contrast-enhanced magnetic resonance imaging. *Circulation* 2000; 102(14):1678-1683.
- (51) Hsu LY, Natanzon A, Kellman P, Hirsch GA, Aletras AH, Arai AE. Quantitative myocardial infarction on delayed enhancement MRI. Part I: Animal validation of an automated feature analysis and combined thresholding infarct sizing algorithm. *J Magn Reson Imaging* 2006; 23(3):298-308.
- (52) Diesbourg LD, Prato FS, Wisenberg G, Drost DJ, Marshall TP, Carroll SE et al. Quantification of myocardial blood flow and extracellular volumes using a bolus injection of Gd-DTPA: kinetic modeling in canine ischemic disease. *Magn Reson Med* 1992; 23(2):239-253.
- (53) Klein C, Nekolla SG, Balbach T, Schnackenburg B, Nagel E, Fleck E et al. The influence of myocardial blood flow and volume of distribution on late Gd-DTPA kinetics in ischemic heart failure. *J Magn Reson Imaging* 2004; 20(4):588-593.
- (54) Judd RM, Lugo-Olivieri CH, Arai M, Kondo T, Croisille P, Lima JA et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. *Circulation* 1995; 92(7):1902-1910.
- (55) Choi CJ, Haji-Momenian S, Dimaria JM, Epstein FH, Bove CM, Rogers WJ et al. Infarct involution and improved function during healing of acute myocardial infarction: the role of microvascular obstruction. *J Cardiovasc Magn Reson* 2004; 6(4):917-925.
- (56) Tong CY, Prato FS, Wisenberg G, Lee TY, Carroll E, Sandler D et al. Measurement of the extraction efficiency and distribution volume for Gd-DTPA in normal and diseased canine myocardium. *Magn Reson Med* 1993; 30(3):337-346.
- (57) Arheden H, Saeed M, Higgins CB, Gao DW, Bremerich J, Wytenbach R et al. Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with <sup>99m</sup>Tc-DTPA autoradiography in rats. *Radiology* 1999; 211(3):698-708.

- (58) Kim RJ, Chen EL, Lima JA, Judd RM. Myocardial Gd-DTPA kinetics determine MRI contrast enhancement and reflect the extent and severity of myocardial injury after acute reperfused infarction. *Circulation* 1996; 94(12):3318-3326.
- (59) Setser RM, Bexell DG, O'Donnell TP, Stillman AE, Lieber ML, Schoenhagen P et al. Quantitative assessment of myocardial scar in delayed enhancement magnetic resonance imaging. *J Magn Reson Imaging* 2003; 18(4):434-441.
- (60) Ricciardi MJ, Wu E, Davidson CJ, Choi KM, Klocke FJ, Bonow RO et al. Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. *Circulation* 2001; 103(23):2780-2783.
- (61) Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. *J Am Coll Cardiol* 2000; 36(6):1985-1991.
- (62) Saeed M, Lund G, Wendland MF, Bremerich J, Weinmann H, Higgins CB. Magnetic resonance characterization of the peri-infarction zone of reperfused myocardial infarction with necrosis-specific and extracellular nonspecific contrast media. *Circulation* 2001; 103(6):871-876.
- (63) Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100(19):1992-2002.
- (64) Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996; 93(2):223-228.
- (65) Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998; 97(8):765-772.
- (66) Costantini CO, Stone GW, Mehran R, Aymong E, Grines CL, Cox DA et al. Frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. *J Am Coll Cardiol* 2004; 44(2):305-312.
- (67) Hombach V, Grebe O, Merkle N, Waldenmaier S, Hoher M, Kochs M et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J* 2005; 26(6):549-557.



- (68) Tarantini G, Razzolini R, Cacciavillani L, Bilato C, Sarais C, Corbetti F et al. Influence of transmural, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty. *Am J Cardiol* 2006; 98(8):1033-1040.
- (69) Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998; 97(8):765-772.
- (70) Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002; 105(4):539-542.
- (71) Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet* 2003; 361(9355):374-379.
- (72) Hunold P, Schlosser T, Vogt FM, Eggebrecht H, Schmermund A, Bruder O et al. Myocardial late enhancement in contrast-enhanced cardiac MRI: distinction between infarction scar and non-infarction-related disease. *AJR Am J Roentgenol* 2005; 184(5):1420-1426.
- (73) Choi KM, Kim RJ, Gubernikoff G, Vargas JD, Parker M, Judd RM. Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. *Circulation* 2001; 104(10):1101-1107.
- (74) Schuijf JD, Kaandorp TA, Lamb HJ, van der Geest RJ, Viergever EP, Van der Wall EE et al. Quantification of myocardial infarct size and transmural extent by contrast-enhanced magnetic resonance imaging in men. *Am J Cardiol* 2004; 94(3):284-288.
- (75) Mahrholdt H, Wagner A, Parker M, Regenfus M, Fieno DS, Bonow RO et al. Relationship of contractile function to transmural extent of infarction in patients with chronic coronary artery disease. *J Am Coll Cardiol* 2003; 42(3):505-512.
- (76) Engblom H, Carlsson MB, Hedstrom E, Heiberg E, Ugander M, Wagner GS et al. The endocardial extent of reperfused first-time myocardial infarction is more predictive of pathologic Q waves than is infarct transmural extent: a magnetic resonance imaging study. *Clin Physiol Funct Imaging* 2007; 27(2):101-108.
- (77) Ito H, Tomooka T, Sakai N, Yu H, Higashino Y, Fujii K et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992; 85(5):1699-1705.

- (78) Ito H, Maruyama A, Iwakura K, Takiuchi S, Masuyama T, Hori M et al. Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996; 93(2):223-228.
- (79) Dreyer WJ, Michael LH, West MS, Smith CW, Rothlein R, Rossen RD et al. Neutrophil accumulation in ischemic canine myocardium. Insights into time course, distribution, and mechanism of localization during early reperfusion. *Circulation* 1991; 84(1):400-411.
- (80) Engler RL. Free radical and granulocyte-mediated injury during myocardial ischemia and reperfusion. *Am J Cardiol* 1989; 63(10):19E-23E.
- (81) Ma XL, Tsao PS, Viehman GE, Lefer AM. Neutrophil-mediated vasoconstriction and endothelial dysfunction in low-flow perfusion-reperfused cat coronary artery. *Circ Res* 1991; 69(1):95-106.
- (82) Gavin JB, Maxwell L, Edgar SG. Microvascular involvement in cardiac pathology. *J Mol Cell Cardiol* 1998; 30(12):2531-2540.
- (83) Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. *Am J Pathol* 1983; 111(1):98-111.
- (84) Kostis JB, Turkevich D, Sharp J. Association between leukocyte count and the presence and extent of coronary atherosclerosis as determined by coronary arteriography. *Am J Cardiol* 1984; 53(8):997-999.
- (85) Gillum RF, Ingram DD, Makuc DM. White blood cell count, coronary heart disease, and death: the NHANES I Epidemiologic Follow-up Study. *Am Heart J* 1993; 125(3):855-863.
- (86) Lowe GD, Machado SG, Krol WF, Barton BA, Forbes CD. White blood cell count and haematocrit as predictors of coronary recurrence after myocardial infarction. *Thromb Haemost* 1985; 54(3):700-703.
- (87) Lima JA, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI. Potential mechanisms. *Circulation* 1995; 92(5):1117-1125.
- (88) Rogers WJ, Jr., Kramer CM, Geskin G, Hu YL, Theobald TM, Vido DA et al. Early contrast-enhanced MRI predicts late functional recovery after reperfused myocardial infarction. *Circulation* 1999; 99(6):744-750.
- (89) Jesel L, Morel O, Ohlmann P, Germain P, Faure A, Jahn C et al. Role of pre-infarction angina and inflammatory status in the extent of microvascular obstruction detected by MRI in myocardial infarction patients treated by PCI. *Int J Cardiol* 2007;



- (90) Kellman P, Arai AE, McVeigh ER, Aletras AH. Phase-sensitive inversion recovery for detecting myocardial infarction using gadolinium-delayed hyperenhancement. *Magn Reson Med* 2002; 47(2):372-383.
- (91) Drew BJ, Pelter MM, Adams MG. Frequency, characteristics, and clinical significance of transient ST segment elevation in patients with acute coronary syndromes. *Eur Heart J* 2002; 23(12):941-947.
- (92) Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342(16):1163-1170.
- (93) Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med* 1984; 311(18):1144-1147.
- (94) The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *N Engl J Med* 1993; 329(22):1615-1622.
- (95) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (96) Brush JE, Jr., Brand DA, Acampora D, Chalmer B, Wackers FJ. Use of the initial electrocardiogram to predict in-hospital complications of acute myocardial infarction. *N Engl J Med* 1985; 312(18):1137-1141.
- (97) Pahlm-Webb U, Pahlm O, Sadanandan S, Selvester RH, Wagner GS. A new method for using the direction of ST-segment deviation to localize the site of acute coronary occlusion: the 24-view standard electrocardiogram. *Am J Med* 2002; 113(1):75-78.
- (98) Rich MW, Imburgia M, King TR, Fischer KC, Kovach KL. Electrocardiographic diagnosis of remote posterior wall myocardial infarction using unipolar posterior lead V9. *Chest* 1989; 96(3):489-493.
- (99) Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol* 2004; 93(3):288-293.
- (100) Freeman MR, Langer A, Wilson RF, Morgan CD, Armstrong PW. Thrombolysis in unstable angina. Randomized double-blind trial of t-PA and placebo. *Circulation* 1992; 85(1):150-157.
- (101) Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction.

Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994; 89(4):1545-1556.

- (102) Charbonnier B, Bernadet P, Schiele F, Thery C, Baudouy M, Bauters C. [Intravenous thrombolysis by recombinant plasminogen activator (rt-PA) in unstable angina. A randomized multicenter study versus placebo]. *Arch Mal Coeur Vaiss* 1992; 85(10):1471-1477.
- (103) Steffenino G, Di Leo M, Orzan F, Bergerone S, Fontana V, Bonzano A et al. Intracoronary streptokinase in unstable angina: a prospective randomised study. *G Ital Cardiol* 1991; 21(11):1159-1166.
- (104) Holland RP, Brooks H. TQ-ST segment mapping: critical review and analysis of current concepts. *Am J Cardiol* 1977; 40(1):110-129.
- (105) Wagner G, Lim T, Gettes L, Gorgels A, Josephson M, Wellens H et al. Consideration of pitfalls in and omissions from the current ECG standards for diagnosis of myocardial ischemia/infarction in patients who have acute coronary syndromes. *Cardiol Clin* 2006; 24(3):331-42, vii.
- (106) Rich MW, Imburgia M. Inotropic response to dobutamine in elderly patients with decompensated congestive heart failure. *Am J Cardiol* 1990; 65(7):519-521.
- (107) Johanson P, Fu Y, Goodman SG, Dellborg M, Armstrong PW, Krucoff MW et al. A dynamic model forecasting myocardial infarct size before, during, and after reperfusion therapy: an ASSENT-2 ECG/VCG substudy. *Eur Heart J* 2005; 26(17):1726-1733.
- (108) Wagner GS, Freye CJ, Palmeri ST, Roark SF, Stack NC, Ideker RE et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. I. Specificity and observer agreement. *Circulation* 1982; 65(2):342-347.
- (109) Ideker RE, Wagner GS, Ruth WK, Alonso DR, Bishop SP, Bloor CM et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarcts. *Am J Cardiol* 1982; 49(7):1604-1614.
- (110) Hindman NB, Schocken DD, Widmann M, Anderson WD, White RD, Leggett S et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. V. Specificity and method of application of the complete system. *Am J Cardiol* 1985; 55(13 Pt 1):1485-1490.
- (111) Anderson WD, Wagner NB, Lee KL, White RD, Yuschak J, Behar VS et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. VI: Identification of screening criteria for non-acute myocardial infarcts. *Am J Cardiol* 1988; 61(10):729-733.

- (112) Freye CJ, Wagner NB, Howe CM, Stack NC, Ideker RE, Selvester RH et al. Evaluation of a QRS scoring system for estimating myocardial infarct size. VIII. Specificity in a control group with left ventricular hypertrophy and proposal of a new scoring system for use with this confounding factor. *J Electrocardiol* 1992; 25(1):19-23.
- (113) Bounous EP, Jr., Califf RM, Harrell FE, Jr., Hinohara T, Mark DB, Ideker RE et al. Prognostic value of the simplified Selvester QRS score in patients with coronary artery disease. *J Am Coll Cardiol* 1988; 11(1):35-41.
- (114) Moon JC, De Arenaza DP, Elkington AG, Tancja AK, John AS, Wang D et al. The pathologic basis of Q-wave and non-Q-wave myocardial infarction: a cardiovascular magnetic resonance study. *J Am Coll Cardiol* 2004; 44(3):554-560.
- (115) Engblom H, Hedstrom E, Heiberg E, Wagner GS, Pahlm O, Arheden H. Size and transmural extent of first-time reperfused myocardial infarction assessed by cardiac magnetic resonance can be estimated by 12-lead electrocardiogram. *Am Heart J* 2005; 150(5):920.
- (116) Engblom H, Wagner GS, Setser RM, Selvester RH, Billgren T, Kasper JM et al. Quantitative clinical assessment of chronic anterior myocardial infarction with delayed enhancement magnetic resonance imaging and QRS scoring. *Am Heart J* 2003; 146(2):359-366.
- (117) MacFarlane PW. In memoriam Jos Willems, MD, PhD (1939-1994). *J Electrocardiol* 1995; 28 Suppl:251-3:251-253.
- (118) Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; 36(3):959-969.
- (119) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (120) Khan IA, Tun A, Wattanasauwan N, Win MT, Hla TA, Hussain A et al. Elevation of serum cardiac troponin I in noncardiac and cardiac diseases other than acute coronary syndromes. *Am J Emerg Med* 1999; 17(3):225-229.
- (121) Bakshi TK, Choo MK, Edwards CC, Scott AG, Hart HH, Armstrong GP. Causes of elevated troponin I with a normal coronary angiogram. *Intern Med J* 2002; 32(11):520-525.
- (122) Larsen AI, Galbraith PD, Ghali WA, Norris CM, Graham MM, Knudtson ML. Characteristics and outcomes of patients with acute myocardial infarction and angiographically normal coronary arteries. *Am J Cardiol* 2005; 95(2):261-263.

- (123) Germing A, Lindstaedt M, Ulrich S, Grewe P, Bojara W, Lawo T et al. Normal angiogram in acute coronary syndrome-preangiographic risk stratification, angiographic findings and follow-up. *Int J Cardiol* 2005; 99(1):19-23.
- (124) Dokainish H, Pillai M, Murphy SA, DiBattiste PM, Schweiger MJ, Lotfi A et al. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol* 2005; 45(1):19-24.
- (125) Hedstrom E, Astrom-Olsson K, Ohlin H, Frogner F, Carlsson M, Billgren T et al. Peak CKMB and cTnT accurately estimates myocardial infarct size after reperfusion. *Scand Cardiovasc J* 2007; 41(1):44-50.
- (126) Zwaka TP, Hombach V, Torzewski J. C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. *Circulation* 2001; 103(9):1194-1197.
- (127) Ballou SP, Lozanski G. Induction of inflammatory cytokine release from cultured human monocytes by C-reactive protein. *Cytokine* 1992; 4(5):361-368.
- (128) Pasceri V, Cheng JS, Willerson JT, Yeh ET. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. *Circulation* 2001; 103(21):2531-2534.
- (129) Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000; 102(18):2165-2168.
- (130) Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336(14):973-979.
- (131) Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998; 98(8):731-733.
- (132) Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994; 331(7):417-424.
- (133) Morrow DA, Rifai N, Antman EM, Weiner DL, McCabe CH, Cannon CP et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. *Thrombolysis in Myocardial Infarction*. *J Am Coll Cardiol* 1998; 31(7):1460-1465.
- (134) de Beer FC, Hind CR, Fox KM, Allan RM, Maseri A, Pepys MB. Measurement of serum C-reactive protein concentration in myocardial ischaemia and infarction. *Br Heart J* 1982; 47(3):239-243.

- (135) Tomoda H, Aoki N. Prognostic value of C-reactive protein levels within six hours after the onset of acute myocardial infarction. *Am Heart J* 2000; 140(2):324-328.
- (136) Anzai T, Yoshikawa T, Shiraki H, Asakura Y, Akaishi M, Mitamura H et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. *Circulation* 1997; 96(3):778-784.
- (137) Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. *J Am Coll Cardiol* 2000; 35(6):1535-1542.
- (138) Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000; 343(16):1139-1147.
- (139) Sano T, Tanaka A, Namba M, Nishibori Y, Nishida Y, Kawarabayashi T et al. C-reactive protein and lesion morphology in patients with acute myocardial infarction. *Circulation* 2003; 108(3):282-285.
- (140) Cusack MR, Marber MS, Lambiase PD, Bucknall CA, Redwood SR. Systemic inflammation in unstable angina is the result of myocardial necrosis. *J Am Coll Cardiol* 2002; 39(12):1917-1923.
- (141) De Sutter J, De Buyzere M, Gheeraert P, Van De WC, Voet J, De Pauw M et al. Fibrinogen and C-reactive protein on admission as markers of final infarct size after primary angioplasty for acute myocardial infarction. *Atherosclerosis* 2001; 157(1):189-196.
- (142) Kojima S, Sakamoto T, Ishihara M, Kimura K, Miyazaki S, Tei C et al. The white blood cell count is an independent predictor of no-reflow and mortality following acute myocardial infarction in the coronary interventional era. *Ann Med* 2004; 36(2):153-160.
- (143) Engler RL, Dahlgren MD, Morris DD, Peterson MA, Schmid-Schonbein GW. Role of leukocytes in response to acute myocardial ischemia and reflow in dogs. *Am J Physiol* 1986; 251(2 Pt 2):H314-H323.
- (144) Wang HR, Li JJ, Huang CX, Jiang H. Fluvastatin inhibits the expression of tumor necrosis factor-alpha and activation of nuclear factor-kappaB in human endothelial cells stimulated by C-reactive protein. *Clin Chim Acta* 2005; 353(1-2):53-60.
- (145) Wang Q, Zhu X, Xu Q, Ding X, Chen YE, Song Q. Effect of C-reactive protein on gene expression in vascular endothelial cells. *Am J Physiol Heart Circ Physiol* 2005; 288(4):H1539-H1545.

- (146) Speidl WS, Zeiner A, Nikfardjam M, Geppert A, Jordanova N, Niessner A et al. An increase of C-reactive protein is associated with enhanced activation of endogenous fibrinolysis at baseline but an impaired endothelial fibrinolytic response after venous occlusion. *J Am Coll Cardiol* 2005; 45(1):30-34.
- (147) Griselli M, Herbert J, Hutchinson WL, Taylor KM, Sohail M, Krausz T et al. C-reactive protein and complement are important mediators of tissue damage in acute myocardial infarction. *J Exp Med* 1999; 190(12):1733-1740.
- (148) Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. *Circulation* 2000; 101(25):2981-2988.
- (149) Spinale FG. Matrix metalloproteinases: regulation and dysregulation in the failing heart. *Circ Res* 2002; 90(5):520-530.
- (150) D'Armiento J. Matrix metalloproteinase disruption of the extracellular matrix and cardiac dysfunction. *Trends Cardiovasc Med* 2002; 12(3):97-101.
- (151) Kim HE, Dalal SS, Young E, Legato MJ, Weisfeldt ML, D'Armiento J. Disruption of the myocardial extracellular matrix leads to cardiac dysfunction. *J Clin Invest* 2000; 106(7):857-866.
- (152) Spinale FG, Coker ML, Thomas CV, Walker JD, Mukherjee R, Hebbar L. Time-dependent changes in matrix metalloproteinase activity and expression during the progression of congestive heart failure: relation to ventricular and myocyte function. *Circ Res* 1998; 82(4):482-495.
- (153) Tyagi SC, Kumar SG, Haas SJ, Reddy HK, Voelker DJ, Hayden MR et al. Post-transcriptional regulation of extracellular matrix metalloproteinase in human heart end-stage failure secondary to ischemic cardiomyopathy. *J Mol Cell Cardiol* 1996; 28(7):1415-1428.
- (154) Soejima H, Ogawa H, Sakamoto T, Miyamoto S, Kajiwara I, Kojima S et al. Increased serum matrix metalloproteinase-1 concentration predicts advanced left ventricular remodeling in patients with acute myocardial infarction. *Circ J* 2003; 67(4):301-304.
- (155) Hirohata S, Kusachi S, Murakami M, Murakami T, Sano I, Watanabe T et al. Time dependent alterations of serum matrix metalloproteinase-1 and metalloproteinase-1 tissue inhibitor after successful reperfusion of acute myocardial infarction. *Heart* 1997; 78(3):278-284.
- (156) Ye S. Polymorphism in matrix metalloproteinase gene promoters: implication in regulation of gene expression and susceptibility of various diseases. *Matrix Biol* 2000; 19(7):623-629.



- (157) Rutter JL, Mitchell TI, Buttice G, Meyers J, Gusella JF, Ozelius LJ et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. *Cancer Res* 1998; 58(23):5321-5325.
- (158) Wagner A, Mahrholdt H, Thomson L, Hager S, Meinhardt G, Rehwald W et al. Effects of time, dose, and inversion time for acute myocardial infarct size measurements based on magnetic resonance imaging-delayed contrast enhancement. *J Am Coll Cardiol* 2006; 47(10):2027-2033.
- (159) Martin TN GBCYSTFJEADHJ. Infarct imaging in a single heart beat: Could LESS be more? *J Am Coll Cardiol* 2003; 41(6):450.
- (160) Laissy JP, Hyafil F, Feldman LJ, Juliard JM, Schouman-Claeys E, Steg PG et al. Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. *Radiology* 2005; 237(1):75-82.
- (161) Gerber BL, Rochitte CE, Melin JA, McVeigh ER, Bluemke DA, Wu KC et al. Microvascular obstruction and left ventricular remodeling early after acute myocardial infarction. *Circulation* 2000; 101(23):2734-2741.
- (162) Gerber BL, Rochitte CE, Melin JA, McVeigh ER, Bluemke DA, Wu KC et al. Microvascular obstruction and left ventricular remodeling early after acute myocardial infarction. *Circulation* 2000; 101(23):2734-2741.
- (163) Anderson ST, Pahlm O, Selvester RH, Bailey JJ, Berson AS, Barold SS et al. Panoramic display of the orderly sequenced 12-lead ECG. *J Electrocardiol* 1994; 27(4):347-352.
- (164) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (165) Engblom H, Wagner GS, Setser RM, Selvester RH, Billgren T, Kasper JM et al. Quantitative clinical assessment of chronic anterior myocardial infarction with delayed enhancement magnetic resonance imaging and QRS scoring. *Am Heart J* 2003; 146(2):359-366.
- (166) Armstrong GP, Barker AN, Patel H, Hart HH. Reference interval for troponin I on the ACS:Centaur assay: a recommendation based on the recent redefinition of myocardial infarction. *Clin Chem* 2002; 48(1):198-199.
- (167) Diabetes. Blood sugar tests, random blood sugar test. 1998-2008 Mayo Foundation for Medical Education and Research . 2008.

Ref Type: Electronic Citation

- (168) Fox KA, Birkhead J, Wilcox R, Knight C, Barth J. British Cardiac Society Working Group on the definition of myocardial infarction. *Heart* 2004; 90(6):603-609.

- (169) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (170) Kwong RY, Schussheim AE, Rekhraj S, Aletras AH, Geller N, Davis J et al. Detecting acute coronary syndrome in the emergency department with cardiac magnetic resonance imaging. *Circulation* 2003; 107(4):531-537.
- (171) Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21(18):1502-1513.
- (172) Bahit MC, Criger DA, Ohman EM, Granger CB, Wagner GS. Thresholds for the electrocardiographic change range of biochemical markers of acute myocardial infarction (GUSTO-IIa data). *Am J Cardiol* 2002; 90(3):233-237.
- (173) Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B et al. ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease; the FRISC II ECG substudy. The Fast Revascularisation during InStability in Coronary artery disease. *Eur Heart J* 2002; 23(1):41-49.
- (174) Sgarbossa EB, Barold SS, Pinski SL, Wagner GS, Pahlm O. Twelve-lead electrocardiogram: the advantages of an orderly frontal lead display including lead -aVR. *J Electrocardiol* 2004; 37(3):141-147.
- (175) Mahrholdt H, Wagner A, Holly TA, Elliott MD, Bonow RO, Kim RJ et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation* 2002; 106(18):2322-2327.
- (176) Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100(19):1992-2002.
- (177) Barbagelata A, Califf RM, Sgarbossa EB, Knight D, Mark DB, Granger CB et al. Prognostic value of predischARGE electrocardiographic measurement of infarct size after thrombolysis: insights from GUSTO I Economics and Quality of Life substudy. *Am Heart J* 2004; 148(5):795-802.
- (178) Kramer CM, Rogers WJ, Jr., Mankad S, Theobald TM, Pakstis DL, Hu YL. Contractile reserve and contrast uptake pattern by magnetic resonance imaging and functional recovery after reperfused myocardial infarction. *J Am Coll Cardiol* 2000; 36(6):1835-1840.
- (179) Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation* 1999; 100(19):1992-2002.



- (180) Hsu LY, Rhoads KL, Holly JE, Kellman P, Aletras AH, Arai AE. Quantitative myocardial perfusion analysis with a dual-bolus contrast-enhanced first-pass MRI technique in humans. *J Magn Reson Imaging* 2006; 23(3):315-322.
- (181) Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol* 2004; 43(12):2253-2259.
- (182) Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. *J Am Coll Cardiol* 2004; 43(12):2253-2259.
- (183) Engblom H, Wagner GS, Setser RM, Selvester RH, Billgren T, Kasper JM et al. Quantitative clinical assessment of chronic anterior myocardial infarction with delayed enhancement magnetic resonance imaging and QRS scoring. *Am Heart J* 2003; 146(2):359-366.
- (184) Engblom H, Hedstrom E, Heiberg E, Wagner GS, Pahlm O, Arheden H. Size and transmural extent of first-time reperfused myocardial infarction assessed by cardiac magnetic resonance can be estimated by 12-lead electrocardiogram. *Am Heart J* 2005; 150(5):920.
- (185) Christiansen JP, Edwards C, Sinclair T, Armstrong G, Scott A, Patel H et al. Detection of myocardial scar by contrast-enhanced cardiac magnetic resonance imaging in patients with troponin-positive chest pain and minimal angiographic coronary artery disease. *Am J Cardiol* 2006; 97(6):768-771.
- (186) Fishbein MC, Maclean D, Maroko PR. The histopathologic evolution of myocardial infarction. *Chest* 1978; 73(6):843-849.
- (187) Iwakura K, Ito H, Kawano S, Okamura A, Kurotobi T, Date M et al. Chronic pre-treatment of statins is associated with the reduction of the no-reflow phenomenon in the patients with reperfused acute myocardial infarction. *Eur Heart J* 2006; 27(5):534-539.
- (188) Yeh ET, Anderson HV, Pasceri V, Willerson JT. C-reactive protein: linking inflammation to cardiovascular complications. *Circulation* 2001; 104(9):974-975.
- (189) Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. *J Intern Med* 2002; 252(4):283-294.
- (190) Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004; 109(21 Suppl 1):II2-10.
- (191) Gabriel AS, Martinsson A, Wretling B, Ahnve S. IL-6 levels in acute and post myocardial infarction: their relation to CRP levels, infarction size, left ventricular systolic function, and heart failure. *Eur J Intern Med* 2004; 15(8):523-528.

- (192) Brinckerhoff CE, Rutter JL, Benbow U. Interstitial collagenases as markers of tumor progression. *Clin Cancer Res* 2000; 6(12):4823-4830.
- (193) Ye S, Dhillon S, Turner SJ, Bateman AC, Theaker JM, Pickering RM et al. Invasiveness of cutaneous malignant melanoma is influenced by matrix metalloproteinase 1 gene polymorphism. *Cancer Res* 2001; 61(4):1296-1298.
- (194) Ghilardi G, Biondi ML, Mangoni J, Leviti S, DeMonti M, Guagnellini E et al. Matrix metalloproteinase-1 promoter polymorphism 1G/2G is correlated with colorectal cancer invasiveness. *Clin Cancer Res* 2001; 7(8):2344-2346.
- (195) Hirata H, Naito K, Yoshihiro S, Matsuyama H, Suehiro Y, Hinoda Y. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter is associated with conventional renal cell carcinoma. *Int J Cancer* 2003; 106(3):372-374.
- (196) Zhu Y, Spitz MR, Lei L, Mills GB, Wu X. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter enhances lung cancer susceptibility. *Cancer Res* 2001; 61(21):7825-7829.
- (197) Singer CF, Marbaix E, Kokorine I, Lemoine P, Donnez J, Eeckhout Y et al. Paracrine stimulation of interstitial collagenase (MMP-1) in the human endometrium by interleukin 1alpha and its dual block by ovarian steroids. *Proc Natl Acad Sci U S A* 1997; 94(19):10341-10345.
- (198) Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2000; 2(4):271-278.
- (199) Perkins GD, McAuley DF, Davies S, Gao F. Discrepancies between clinical and postmortem diagnoses in critically ill patients: an observational study. *Crit Care* 2003; 7(6):R129-R132.
- (200) Spiliopoulou C, Papadodima S, Kotakidis N, Koutselinis A. Clinical diagnoses and autopsy findings: a retrospective analysis of 252 cases in Greece. *Arch Pathol Lab Med* 2005; 129(2):210-214.
- (201) Hess OM, Schneider J, Nonogi H, Carroll JD, Schneider K, Turina M et al. Myocardial structure in patients with exercise-induced ischemia. *Circulation* 1988; 77(5):967-977.
- (202) McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ et al. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation* 2003; 108(1):54-59.
- (203) Myerburg RJ, Interian A, Jr., Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997; 80(5B):10F-19F.

- (204) Liberthson RR, Nagel EL, Hirschman JC, Nussenfeld SR, Blackbourne BD, Davis JH. Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death. *Circulation* 1974; 49(5):790-798.
- (205) Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. *Circulation* 1995; 92(7):1701-1709.
- (206) Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S et al. Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006; 113(23):2733-2743.
- (207) Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I et al. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2005; 111(2):186-193.
- (208) Moon JC, McKenna WJ, McCrohon JA, Elliott PM, Smith GC, Pennell DJ. Toward clinical risk assessment in hypertrophic cardiomyopathy with gadolinium cardiovascular magnetic resonance. *J Am Coll Cardiol* 2003; 41(9):1561-1567.
- (209) Mark PB, Johnston N, Groenning BA, Foster JE, Blyth KG, Martin TN et al. Redefinition of uremic cardiomyopathy by contrast-enhanced cardiac magnetic resonance imaging. *Kidney Int* 2006; 69(10):1839-1845.
- (210) Froelicher VF, Thompson AJ, Longo MR, Jr., Triebwasser JH, Lancaster MC. Value of exercise testing for screening asymptomatic men for latent coronary artery disease. *Prog Cardiovasc Dis* 1976; 18(4):265-276.
- (211) Thaulow E, Erikssen J, Sandvik L, Erikssen G, Jorgensen L, Cohn PF. Initial clinical presentation of cardiac disease in asymptomatic men with silent myocardial ischemia and angiographically documented coronary artery disease (the Oslo Ischemia Study). *Am J Cardiol* 1993; 72(9):629-633.
- (212) Cohn PF, Fox KM, Daly C. Silent myocardial ischemia. *Circulation* 2003; 108(10):1263-1277.
- (213) Yano K, MacLean CJ. The incidence and prognosis of unrecognized myocardial infarction in the Honolulu, Hawaii, Heart Program. *Arch Intern Med* 1989; 149(7):1528-1532.
- (214) Geft IL, Fishbein MC, Hashida J, Ninomiya K, Nishizawa S, Haendchen R et al. Effects of late coronary artery reperfusion after myocardial necrosis is complete. *Am Heart J* 1984; 107(4):623-629.

- (215) Barbier CE, Bjerner T, Johansson L, Lind L, Ahlstrom H. Myocardial scars more frequent than expected: magnetic resonance imaging detects potential risk group. *J Am Coll Cardiol* 2006; 48(4):765-771.
- (216) Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. The FRISC study group. *Circulation* 1996; 93(9):1651-1657.
- (217) Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996; 335(18):1342-1349.
- (218) Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prognostic significance of admission troponin T concentrations in patients with myocardial infarction. *Circulation* 1996; 94(6):1291-1297.
- (219) Stubbs P, Collinson P, Moseley D, Greenwood T, Noble M. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. *BMJ* 1996; 313(7052):262-264.
- (220) Kontos MC, Shah R, Fritz LM, Anderson FP, Tatum JL, Ornato JP et al. Implication of different cardiac troponin I levels for clinical outcomes and prognosis of acute chest pain patients. *J Am Coll Cardiol* 2004; 43(6):958-965.
- (221) Kaandorp TA, Bax JJ, Lamb HJ, Viergever EP, Boersma E, Poldermans D et al. Which parameters on magnetic resonance imaging determine Q waves on the electrocardiogram? *Am J Cardiol* 2005; 95(8):925-929.
- (222) Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ et al. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007; 99(5):657-660.
- (223) Gaspoz JM, Lee TH, Cook EF, Weisberg MC, Goldman L. Outcome of patients who were admitted to a new short-stay unit to "rule-out" myocardial infarction. *Am J Cardiol* 1991; 68(2):145-149.
- (224) Gaspoz JM, Lee TH, Weinstein MC, Cook EF, Goldman P, Komaroff AL et al. Cost-effectiveness of a new short-stay unit to "rule out" acute myocardial infarction in low risk patients. *J Am Coll Cardiol* 1994; 24(5):1249-1259.
- (225) Gibler WB, Runyon JP, Levy RC, Sayre MR, Kacich R, Hattemer CR et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. *Ann Emerg Med* 1995; 25(1):1-8.
- (226) Peski-Oosterbaan AS, Spinhoven P, Koch GC, van der Does AJ, Padmos I, Bruschke AV. [Unexplained non-cardiac chest pain; its prevalence and natural course]. *Ned Tijdschr Geneesk* 1998; 142(45):2468-2472.

- (227) Sekhri N, Feder GS, Junghans C, Hemingway H, Timmis AD. How effective are rapid access chest pain clinics? Prognosis of incident angina and non-cardiac chest pain in 8762 consecutive patients. *Heart* 2007; 93(4):458-463.
- (228) Kinch JW, Ryan TJ. Right ventricular infarction. *N Engl J Med* 1994; 330(17):1211-1217.
- (229) Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-dimensional echocardiography. *N Engl J Med* 1981; 305(6):297-302.
- (230) Weinreich DJ, Burke JF, Pauletto FJ. Left ventricular mural thrombi complicating acute myocardial infarction. Long-term follow-up with serial echocardiography. *Ann Intern Med* 1984; 100(6):789-794.
- (231) Keating EC, Gross SA, Schlamowitz RA, Glassman J, Mazur JH, Pitt WA et al. Mural thrombi in myocardial infarctions. Prospective evaluation by two-dimensional echocardiography. *Am J Med* 1983; 74(6):989-995.
- (232) Kalra A, Jang IK. Prevalence of early left ventricular thrombus after primary coronary intervention for acute myocardial infarction. *J Thromb Thrombolysis* 2000; 10(2):133-136.
- (233) Somers MP, Brady WJ, Bateman DC, Mattu A, Perron AD. Additional electrocardiographic leads in the ED chest pain patient: right ventricular and posterior leads. *Am J Emerg Med* 2003; 21(7):563-573.
- (234) McClelland AJ, Owens CG, Menown IB, Lown M, Adgey AA. Comparison of the 80-lead body surface map to physician and to 12-lead electrocardiogram in detection of acute myocardial infarction. *Am J Cardiol* 2003; 92(3):252-257.
- (235) Madsen LH, Christensen G, Lund T, Serebruany VL, Granger CB, Hoen I et al. Time course of degradation of cardiac troponin I in patients with acute ST-elevation myocardial infarction: the ASSENT-2 troponin substudy. *Circ Res* 2006; 99(10):1141-1147.

# 12 Appendix

## 12.1 Selvester Score

Complete 50-Criteria, 31-point QRS Scoring System*										
Lead	Maximum Lead Points	Criteria	Points	V1			V3			
				Anterior (1)	Any Q (1)	(1)	(1)	{ Any Q (1) R ≥ 20ms (2) R ≤ 0.2mV (1)	(3)	
I	(2)	Q ≥ 30ms (1) R/Q ≤ 1 (1) R ≤ 0.2mV (1)	(1) (1) (1)	Posterior (4)	R/S ≥ 1 (1)	(1)		V4 (3)	Q ≥ 20ms (1)	
					{ R ≥ 50ms (2) R ≤ 1.0mV (2) R ≥ 40ms (1) R ≤ 0.6mV (1)	(2) (2) (1) (1)		{ R/S ≤ 0.5 (2) R/Q ≤ 0.5 (2) R/S ≤ 1 (1) R/Q ≤ 1 (1) R ≤ 0.7mV (1)	(2) (2) (1) (1) (1)	
II	(2)	{ Q ≥ 40ms (2) Q ≥ 30ms (1)	(2) (1)		Q and S ≤ 0.3mV (1)	(1)		V5 (3)	Q ≥ 30ms (1)	
aVL	(2)	Q ≤ 30ms (1) R/Q ≥ 1 (1)	(1) (1)	V2	Anterior (1)	{ Any Q (1) R ≤ 10ms (1) R ≤ 0.1mV (1) R ≥ RV1 mV (1)	(1) (1) (1) (1)		{ R/S ≤ 1 (2) R/Q ≤ 1 (2) R/S ≤ 2 (1) R/Q ≤ 2 (1) R ≤ 0.7mV (1)	(2) (2) (1) (1) (1)
aVF	(5)	{ Q ≤ 50ms (3) Q ≥ 40ms (2) Q ≥ 30ms (1)  { R/Q ≤ 1 (2) R/Q ≥ 2 (1)	(3) (2) (1)  (2) (1)		Posterior (4)	R/S ≥ 1.5 (1)	(1)		V6 (3)	Q ≥ 30ms (1)
					{ R ≥ 60ms (2) R ≥ 2.0mV (2) R ≥ 50ms (1) R ≥ 1.5mV (1)	(2) (2) (1) (1)		{ R/S ≤ 1 (2) R/Q ≤ 1 (2) R/S ≤ 3 (1) R/Q ≤ 3 (1) R ≤ 0.6mV (1)	(2) (2) (1) (1) (1)	
					Q and S ≤ 0.4mV (1)	(1)				

## 12.2 Information sheet for patients/ volunteers in clinical research project

THIS SHEET HAS BEEN APPROVED BY THE WEST ETHICS COMMITTEE

### INFORMATION SHEET FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

#### Patient's Summary

#### The Role of Cardiac magnetic Resonance Imaging (CMR) in ACS (ACS)

We would like to invite you to take part in a study to assess the role of a special scan called **Cardiac Magnetic Resonance Imaging (CMR)** with an injection of dye (contrast) called **gadolinium** in the diagnosis of **Acute Coronary Syndromes (ACS)**. **ACS** is a new term that includes a range of heart muscle damage from angina to a heart attack. You have been invited to take part in this study because it is the first time you have been admitted to hospital with chest pain, which is suspected to have come from the heart.

**CMR** is a new type of scan that does not rely on radiation to create the pictures. The machine is shaped like a large tunnel and open at both ends. The scanner contains the magnet, which enables the images of your heart to be obtained. 5% of patients do not wish to enter the scan because they don't like confined spaces (claustrophobia).

**Gadolinium** looks clear like water, is non-radioactive and is many times safer than the iodine type contrast used in X-Ray scans. After it is injected into a vein, **gadolinium** accumulates in the abnormal tissue and these areas become very bright (enhanced), it is then rapidly cleared from the body by the kidneys. A few side effects, such as headache, nausea, light headedness and local burning can occur. Very rarely (less than one in a hundred thousand), patients are allergic to **gadolinium** when they develop a rash and/ or swollen lips. If this occurs you will be assessed by the doctor supervising the scan, or if you have left the hospital contact your GP.

On arrival at the **Clinical Research Initiative (CRI)** a radiographer will go through a safety checklist and make sure that all magnetic objects (e.g. jewellery and bankcards) have been removed. Following this you will be asked to sign the consent form. Once you have changed into a hospital gown you will then be asked to lie flat on the bed that will move into the scanner. A small plastic cannula (similar to that used when putting up a drip) will be inserted into your vein to allow us to take a blood sample and give you the **gadolinium**. A doctor will insert the cannula and 30 mls of blood (about 3 tablespoonfuls) will be taken. This blood will be used to check your liver and kidney function and to detect the concentration of a substance called BNP (a measure of how well your heart pumps). You will need to wear a pair of headphones, allowing you to listen to music of your choice (you are welcome to bring your own CD) and to allow us to communicate with you throughout the scan. The headphones are also necessary because of the loud knocking noise that occurs when the pictures are being taken. You will be given an emergency buzzer and very quickly taken out of the scanner should it be necessary. During the scan you will be asked to hold your breath for about 8 seconds, on separate occasions to improve the quality of the pictures. The scan will last approximately 45 minutes.

You will be invited to return to the Western Infirmary on 3 further occasions. After 4 weeks, 6 months and 1 year for a clinical assessment, repeat scan and further blood tests. Each visit will last approximately 1 hour and will take place in the **(CRI)** located on **level 4** of the **Western Infirmary, Glasgow**.

You are not obliged to take part in the current study but if you do decide to take part then you will be asked to give your written consent. If you do not wish to participate then your care will not be affected in any way. You may withdraw from the study at any time. Your GP will be informed of your participation in the study. If you are, or are likely to be, pregnant then we advise that you do not take part in the study. It should be noted that your participation may not be of direct benefit to you, but could help in the development of diagnostic tests and treatments for the benefit of future patients. We may from time to time wish to obtain information from your hospital medical notes and we therefore ask you to release this on the understanding that, like any other details, it will be kept confidential. If you have any questions or concerns about this study please contact Professor Dargie or Dr Thomas Martin at 0141 211 8527.



WEST ETHICS COMMITTEE

FORM OF CONSENT FOR PATIENTS/VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project:

The Role of Cardiac magnetic Resonance Imaging (CMR) in ACS

By signing this form you give consent to your participation in the project whose title is at the top of this page. You should have been given a complete explanation of the project to your satisfaction and have been given the opportunity to ask questions. You should have been given a copy of the patient information sheet approved by the West Ethics Committee to read and to keep. Even though you have agreed to take part in the research procedures you may withdraw this consent at any time without the need to explain why and without any prejudice to your care.

Consent:

I,.....(PRINT)

of.....

give my consent to the research procedures above, the nature, purpose and possible consequences of which have been described to me


by.....

Patient's signature.....Date.....

Doctor's signature.....



12.3 Personal Health Record



UNIVERSITY  
of  
GLASGOW

THE MIRAGE (Book)

Parent Letter

Personal Health Record

(All information is confidential)

Please answer every question, as far as you can, (except those you are told to skip) and circle the box which applies to you. We cannot use those questions that you have completely blank. If the answer in your case is "No" or "I don't know" you still need to show this on the paper. If you need any help, or have any questions, please ask our nurse who will check through the record with you.

If you are asked for the day of the illness and you do not know the month please just put the year.

1. Personal History

(a) Please circle the appropriate box: Male ☐ Female ☐

(b) Date of birth: day ☐ month ☐ year ☐

5. What race are you?

Please tick the appropriate box (+)

White / Caucasian	
Chinese	
Asian	
Black	
Hispanic	

c. How do you and your household occupy your accommodation?

Please tick the appropriate box (+)

Home owner	
Renting - private	
Local Authority / Housing association	

THE MIRAGE (Story)

2. Family History

Do you have a family history of heart disease?

☐ Yes ☐ No

If you please complete as best as possible

Relationship	Diagnosis	Age at diagnosis	Alive (yes/no)
Mother			
Father			
Brother			
Sister			
Grandparents			
Other			

3. Past Medical History

Have you ever had a stroke or heart attack?

☐ Yes ☐ No

Have you been told by a doctor that you have cardiac problems / heart problems in your leg?

☐ Yes ☐ No

4. Angina

Have you ever been told by a doctor that you have angina?

☐ Yes ☐ No

If **no** then please go on to next question

If **yes**...

a. Have you had a heart attack?

☐ Yes ☐ No

b. Have you had an angina?

☐ Yes ☐ No

c. Do you take any medication for angina?

☐ Yes ☐ No

d. Have you been admitted to hospital with chest pain before?

☐ Yes ☐ No

5. Blood Pressure

Have you ever been told by a doctor that you have high blood pressure?

☐ Yes ☐ No

If **no** then please go on to next question

If **yes**...

Do you take any medication for high blood pressure?

☐ Yes ☐ No

If **no** please list medication and how long (years) you have been taking it:

Medication	Duration (years)

THE MIRAGE (Story)

6. Diabetes

Have you ever been told by a doctor that you have diabetes?

☐ Yes ☐ No

If you have diabetes then how is it treated (please circle)?

Diet      Tablets      Insulin

How long have you had it for (years)? .....

7. Cholesterol

Have you ever been told by your doctor that you have high cholesterol?

☐ Yes ☐ No

If **no** then please go on to next question

If **yes**...

If you have high cholesterol then how is it treated (please circle)?

Diet      Tablets

How long have you had it for (years)? .....

- 200 -

## 8. Chest Pain

a. In one word try to describe the chest pain or discomfort you experienced

b. Where did you get the pain or discomfort?  
Mark the place(s) with X on the diagram



c. Did the pain go anywhere else?  
Mark where on the diagram with an arrow or write below

d. Approximately how long (in minutes) did the pain or discomfort last for?

e. What made the pain go away?

f. Please mark on the line below how severe the pain or discomfort was (10 being the worst pain imaginable)

1 5 10

g. Did you feel short of breath?

☐ Yes ☐ No

h. Did you feel sick/nauseous?

☐ Yes ☐ No

i. Were you sweating or clammy?

☐ Yes ☐ No

## 9. Cigarette smoking

b. How many cigarettes smoked regularly?

☐ Yes - Go to Question 17  
☐ No - Go to Question 17

17. If you have smoked regularly

a. At what age did you start smoking?  Yes old

b. Do you still smoke?

☐ Yes ☐ No - at what age did you stop smoking?  Yes

c. How many days a week do you / did you smoke?

d. How many cigarettes do you / did you smoke on each of these days?

## 10. Alcoholic drinks

15. (a) Have you ever taken alcoholic drinks?

☐ Yes ☐ No - if No please go to end of questionnaire

(b) Do you take alcoholic drinks at present

☐ Yes ☐ No ☐ seldom

(c) Think back carefully over the last seven days. Please write in the table over the page exactly what alcoholic drinks you have consumed on each day during the past week.

Try to remember where you were and who you were with on each day. That may help you remember what you have had to drink.

For each day, write in how much you have drunk:

(a) the number of pints of low-alcohol (non-alcoholic) beer, lager, etc.  
(b) the number of pints of beer, lager, shandy, cider, stout, etc.  
(c) the number of single glasses of whisky, vodka, gin, rum, etc.  
(d) the number of single glasses of wine, sherry, Mirtan, port, etc.

	Pints of low-alcohol (non-alcoholic) beer, etc.	Pints of beer, lager, shandy, etc.	Single glasses of whisky, etc.	Single glasses of wine, etc.
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

(d) Would you say that last week was fairly typical of what you usually have to drink in one week?

☐ Yes ☐ No

(e) If last week was not typical, would you normally drink more or less in a week?

☐ More ☐ Less



Thank You for completing this questionnaire.

Office Use Only

Checked By:

Print Name:

Date: / /

# 12.4 MRI safety Questionnaire

## CRI MRI UNIT Safety Checklist and Investigation Details - *PATIENTS*

Patient Name		Date of Scan:	
Address: Postcode		Referring Clinician: Location:	
Date of Birth:		Weight (kg):	Height (cm):
Hospital No.			

SAFETY QUESTIONS		YES	NO			YES	NO
Have they:				Have they:			
A cardiac pacemaker				Any dentures or hearing aids?			
An artificial heart valve				Any hairclips and jewellery?			
An aneurysm clip				Any tattoos or permanent makeup?			
A bladder implant				Any body piercing?			
An ear implant				Any hairpieces?			
A pain relief implant				Removed their watch, credit cards and emptied their pockets?			
A time release drug dispenser							
An eye prostheses							
Any other implants							
Have they ever:				Ladies only:			
Done welding or grinding?				Could you be pregnant or breast feeding?			
Had metal enter their bodies				Have you been sterilised or have you an IUD fitted?			
Had heart trouble?							
Had an operation on their head?							
Had any artificial joints or screws or pins or plates for broken bones?				Do you have asthma hayfever or any allergies that you know of?			
Had any other surgical operations?							
List.....							

I confirm that the answers to the above safety questions are correct	
I also confirm that I will accept a contrast agent injection if required.	
Signature of patient*parent/guardian	Date ____/____/____
*Patient only if over 16	

Signature of Authorised Scanning Staff Member

If the patient is comatose, young or confused:

- have you confirmed with the Supervising Radiologist that they are safe to image? (please ring) YES NO
- If the patient is unable to sign please state why: \_\_\_\_\_

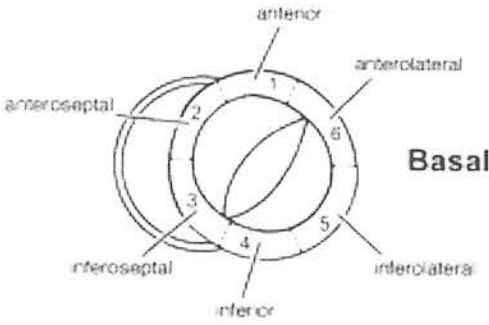
The Supervising Clinician should countersign here if no clear history of implants or operations, can be obtained.

• Note the implant or operation here: \_\_\_\_\_

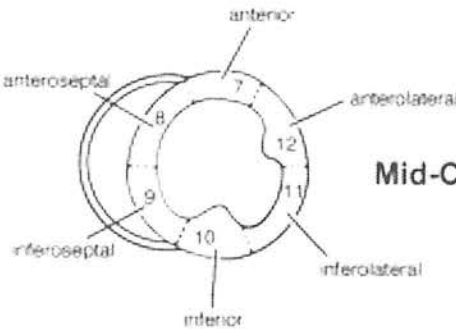
  

The Supervising Clinician should sign here if they now consider the scan to be completely safe.	
---	--

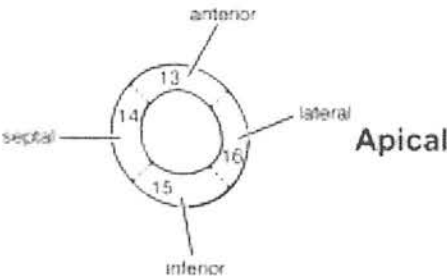
# 12.5 AHA/ ESC 17 segment model used to determine infarct location



**Basal**

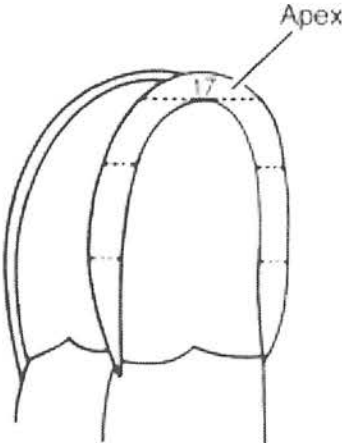


**Mid-Cavity**

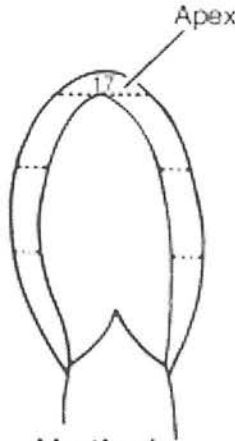


**Apical**

**Short Axis (SA)**



**Horizontal Long Axis (HLA)**  
(4 Chamber)



**Vertical Long Axis (VLA)**  
(2 Chamber)

## 12.6 Abstracts from this thesis

### **Infarct imaging in a single heart beat: Could LESS be more?**

Martin TN, Groenning BA, Chung YC, Steedman T, Foster JE, Elliott AT, Dargie HJ

J Am Coll Cardiol. 2003 Mar 19;41(6 Suppl B):450

### **A single troponin I concentration measured 12 hours after onset of chest pain accurately reflects infarct size as measured by gadolinium-DTPA late enhancement magnetic resonance imaging**

Martin TN, Groenning BA, Steedman T, Foster JE, Elliott AT, Dargie HJ.

J Am Coll Cardiol. 2003 Mar 19;41(6 Suppl B):380-1

### **Validation of the 12-lead admission ECG in patients with acute chest pain for diagnosis of myocardial infarction by late contrast enhanced magnetic resonance imaging.**

Martin TN, Wagner GS, Steedman T, Foster JE, Elliott AT, Dargie HJ, Groenning BA.

Eur Heart J 2003;8 (abstr.suppl.):92

### **Validation of the ECG Selvester Score for assessment of infarct size by late contrast enhanced magnetic resonance imaging**

Thomas Martin, Bjoern Groenning, Galen Wagner, Tracey Steedman, John Foster, Alex

Elliott, Henry Dargie

Society of Cardiovascular Magnetic Resonance Imaging. J Cardiovasc Magn Res 2003

**Usefulness of CRP in detecting higher risk patterns of myocardial infarction defined by contrast enhanced magnetic resonance imaging**

Thomas N. Martin, Naveed Sattar, Robin Weir, Simon Martin, Nirosha Gunitillake, Charles Maynard, Andrew Flapan, Henry Dargie.

American College of Cardiology, March 2008.

**The detection of myocardial scar by ceMRI in patients with TnI positive chest pain and minimal angiographic coronary artery disease**

Thomas N. Martin, Galen Wagner, Bjoern Groenning, Robin Weir, Andrew Flapan, Henry Dargie.

Society of Cardiovascular Magnetic Resonance Imaging, Feb 2008. J Cardiovasc Magn Res  
2008 Feb

**Validation of electrocardiographic and biochemical estimates of first acute myocardial infarct size using cardiac magnetic resonance imaging**

Thomas N. Martin, Galen Wagner, Allan Pettigrew, Bjoern Groenning, Robin Weir, Charles Maynard, Andrew Flapan, Henry Dargie.

British Cardiac Society, June 2008

## 12.7 Full publications from this thesis

### **ST-deviation analysis of the admission 12-lead ECG as an aid to early diagnosis of acute myocardial infarction using a cardiac magnetic resonance imaging gold standard**

Thomas N Martin, Bjoern A Groenning, Heather M Murray, Tracey Steedman, John E Foster, Alex T Elliot, Henry J Dargie,, Ron Selvester, Olle Pahlm, Galen Wagner .

J Am Coll Cardiol. 2007 Sep 11;50 (11):1021-8.

### **Myocardial infarct quantification: is magnetic resonance imaging ready to serve as a gold standard for electrocardiography?**

Engblom H, Arheden H, Foster JE, Martin TN.

J Electrocardiol. 2007 Jul;40(3):243-5.

### **Diagnosing Acute Myocarditis using Cardiac Magnetic Resonance Imaging**

Thomas N Martin, Bjoern Groenning and Henry J Dargie

Eur Heart J.2006 Feb;27(4):468

### **Matrix Metalloproteinase-1 Promoter Polymorphisms and changes in Left Ventricular Volume following Acute Myocardial Infarction**

Thomas N. Martin, Dawn E. Penney, Jamie A Smith, Bjoern A. Groenning, Henry J Dargie, Graham S. Hillis.

Am J Cardiol. 2004 Oct 15;94(8):1044-6